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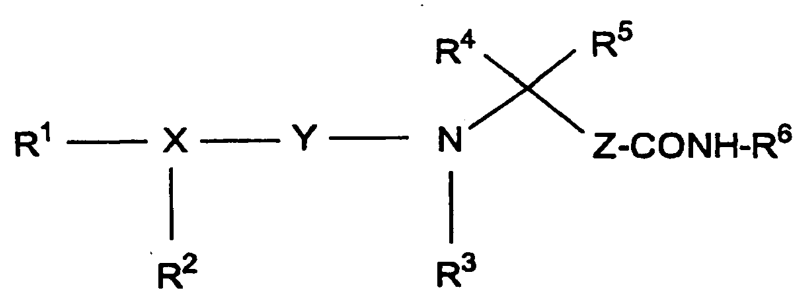
(57) Abstract

The compound of the present invention is useful as a medicament for prophylactic and therapeutic treatment of MMP- or TNF α-mediated diseases.



DESCRIPTION

MMP INHIBITOR

Technical Field

The present invention relates to new compounds and pharmaceutically acceptable salts thereof.

More particularly, it relates to new compounds and pharmaceutically acceptable salts thereof which are useful as inhibitors of matrix metalloproteinases (hereinafter to be referred to as MMP) or the production of tumor necrosis factor α (hereinafter to be referred to as TNFα), to pharmaceutical compositions comprising the same, to use of the same as medicaments, and to methods for using the same therapeutically in the treatment and/or the prevention of MMP- or TNF α-mediated diseases.

Background Art

Some piperazine compounds to be useful as metalloproteinase inhibitors, or the like are known (WO 97/20824, etc.).

Disclosure of the Invention

One object of the present invention is to provide new and useful compounds and pharmaceutically acceptable salts thereof, and to provide a process for preparing said new compound and salts thereof, which have pharmacological activities such as MMP- or TNFα-inhibitory activity and the like.

Another object of the present invention is to provide a pharmaceutical composition comprising, as an active ingredient, said compound or a pharmaceutically acceptable salt thereof.

A further object of the present invention is to provide use of said compounds and pharmaceutically acceptable salts thereof as medicaments for prophylactic and therapeutic treatment of MMP- or TNF α-mediated diseases.

A still further object of the present invention is to provide a method for using the same for the treatment and/or the prevention of MMP- or TNF α-mediated diseases in mammals, especially humans.

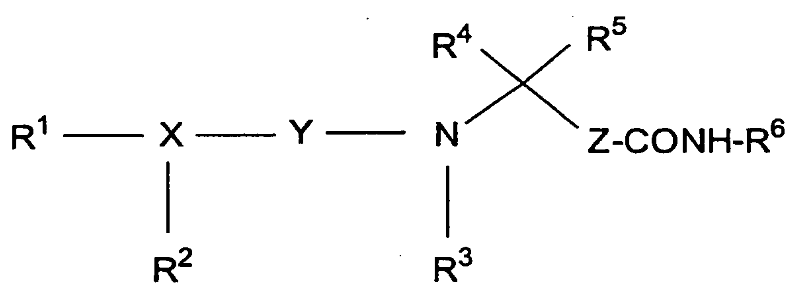
The compounds of the present invention have inhibitory activity on MMP or the production of TNFα, and are useful for the treatment and/or prevention of diseases such as stroke, arthritis, cancer, tissue ulceration, decubitus ulcer, restenosis, periodontal disease, epidermolysis bullosa, scleritis, psoriasis and

other diseases characterized by matrix metalloproteinase activity, as well as AIDS, sepsis, septic shock and other diseases caused by the production of TNF α.

There are a number of structurally related metalloproteases which effect the breakdown of structural proteins. Matrix-degrading metallo- proteases, such as gelatinase (MMP-2, MMP-9), stromelysin (MMP-3) and collagenase (MMP-1, MMP-8, MMP-13), are involved in tissue matrix degradation and have been implicated in many pathological conditions involving abnormal connective tissue and basement membrane matrix metabolism, such as arthritis (e.g., osteoarthritis and rheumatoid arthritis), cerebral disease (e.g., stroke, etc.), tissue ulceration (e.g., corneal, epidermal and gastric ulcerations), abnormal wound healing, periodontal disease, bone disease (e.g., Paget's disease and osteoporosis), tumor metastasis or invasion and HIV-infection.

A tumor necrosis factor is recognized to be involved in many infections and autoimmune diseases. Furthermore, it has been shown that TNF is the prime mediator of the inflammatory response seen in sepsis and septic shock.

The object compounds of the present invention are novel and can be represented by the following formula (I):



(I)

wherein

R^1 is halogen, nitro, lower alkoxy, optionally substituted aryloxy, arylthio, aroyl, heterocyclic-oxy, optionally substituted aryl or optionally substituted heterocyclic group;

R^2 is hydrogen or halogen;

R^3 is hydrogen or lower alkyl;

R^4 and R^5 are independently hydrogen, lower alkyl, or lower cycloalkyl, or R^4 and R^5 are combined together to form lower alkylene, which is optionally interrupted by oxygen, sulfur, sulfinyl, sulfonyl or optionally mono-substituted nitrogen;

R^6 is hydroxy or protected hydroxy;

X is aryl or heterocyclic group;

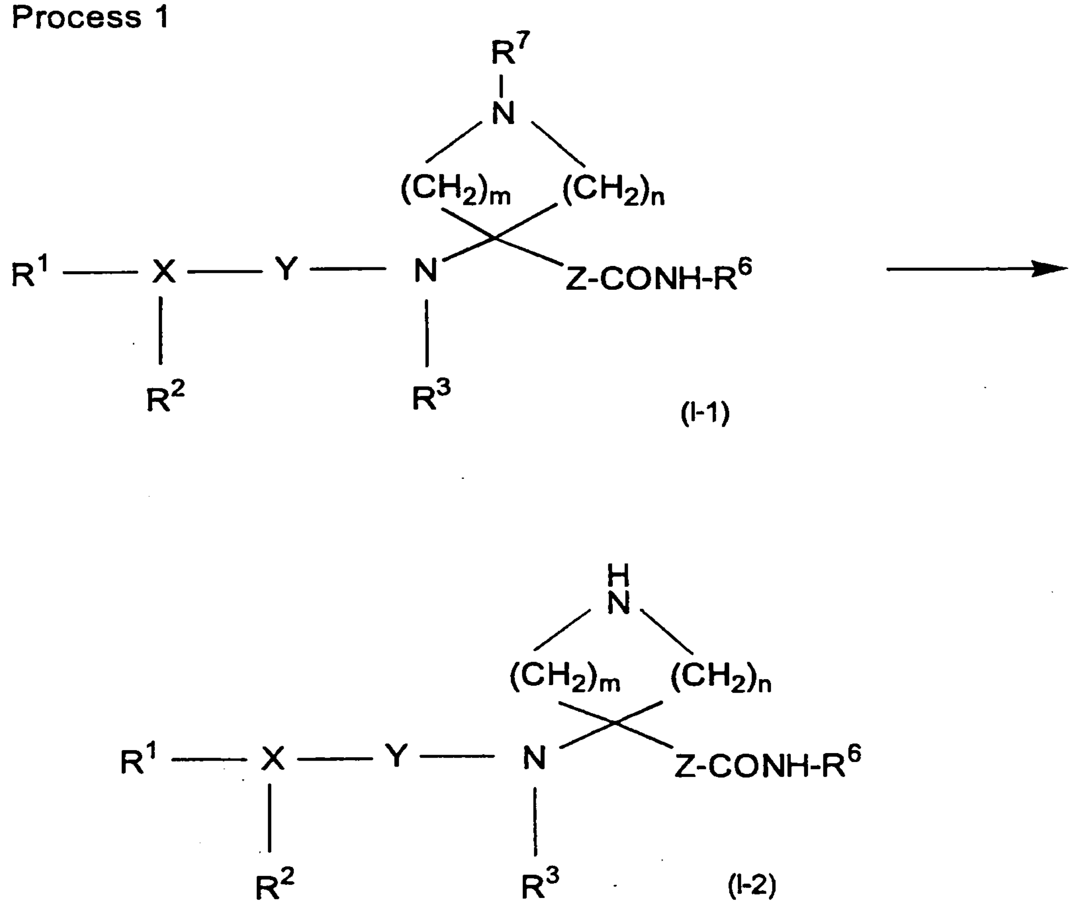
Y is carbonyl or sulfonyl; and

Z is lower alkylene;

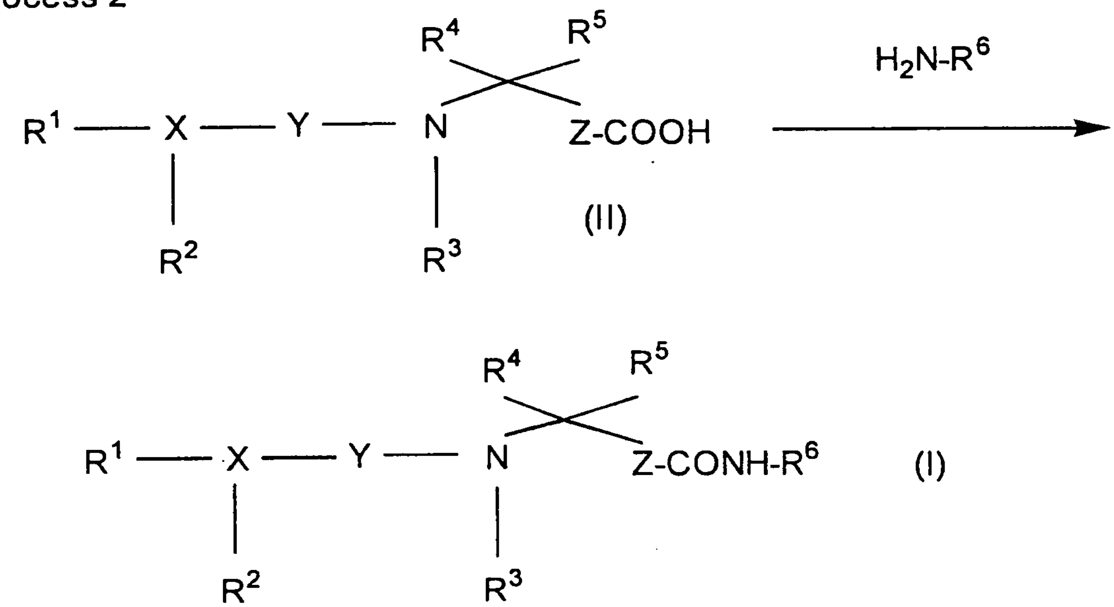
and a pharmaceutically acceptable salt thereof.

The object compounds of the present invention can be prepared by the following processes.

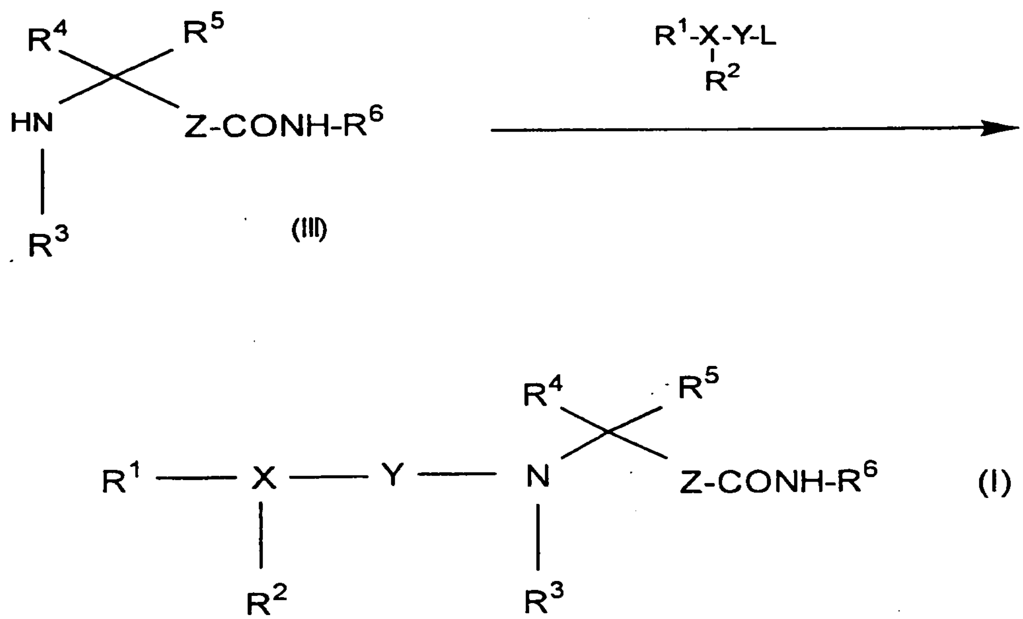
Process 1



Process 2



Process 3



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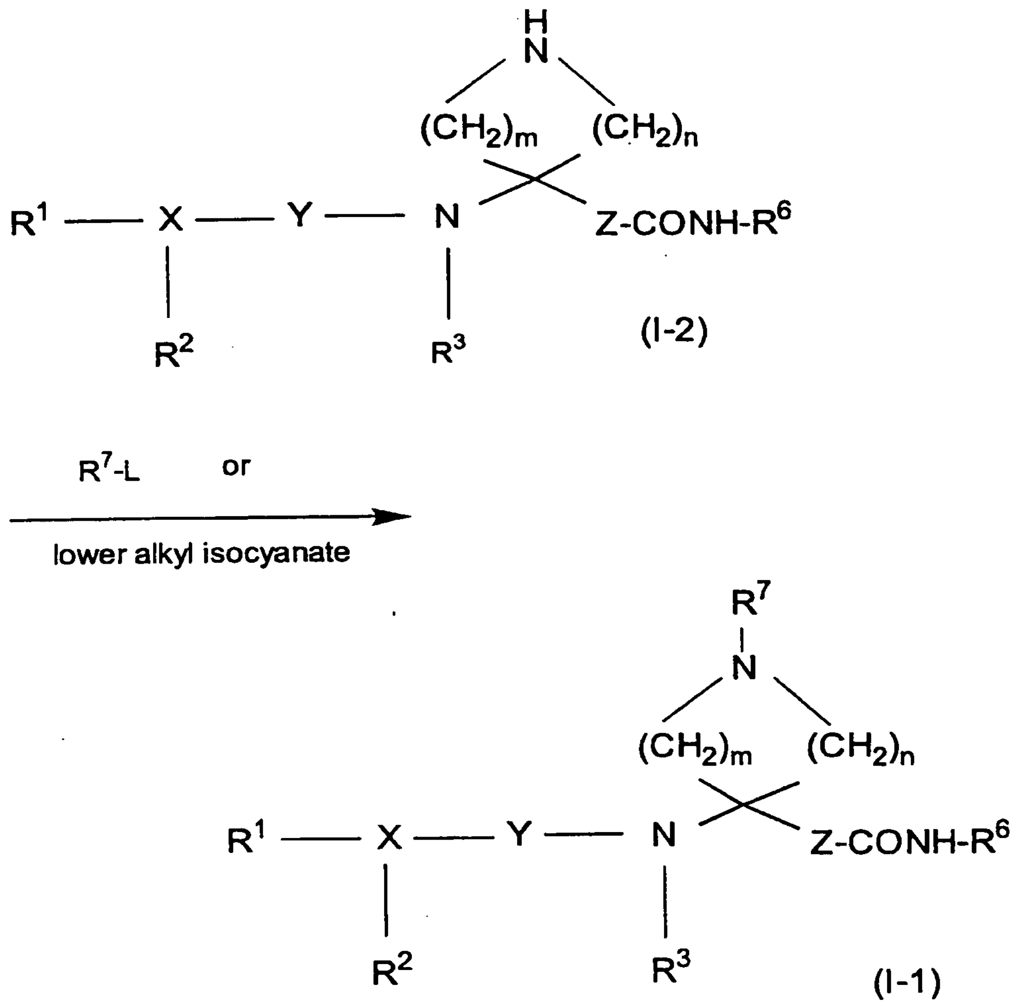
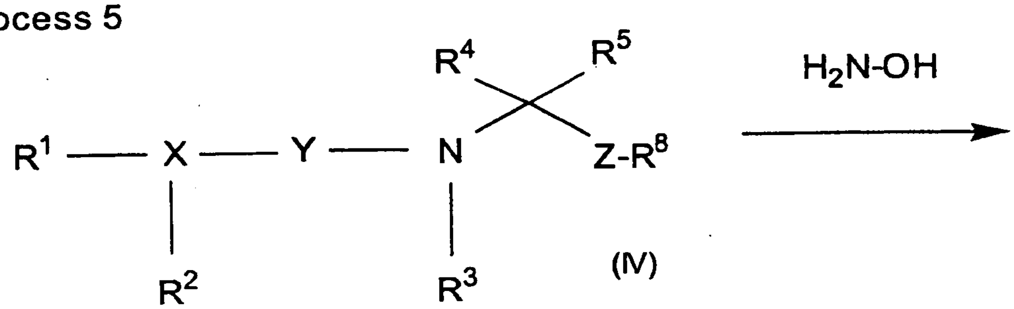
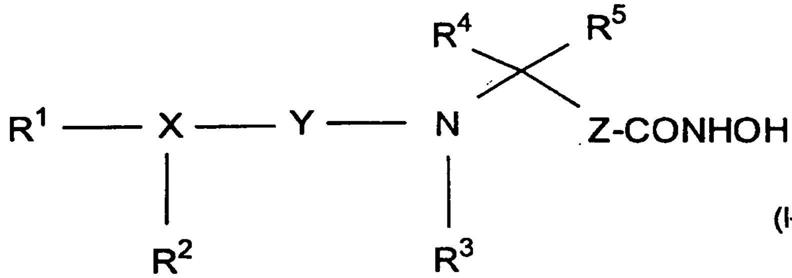


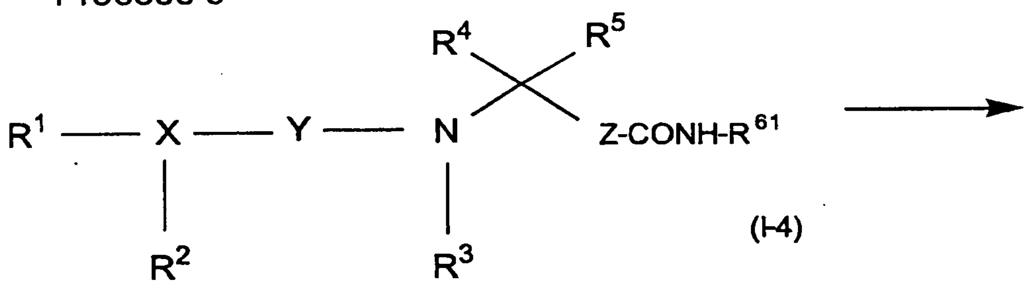
Process 5



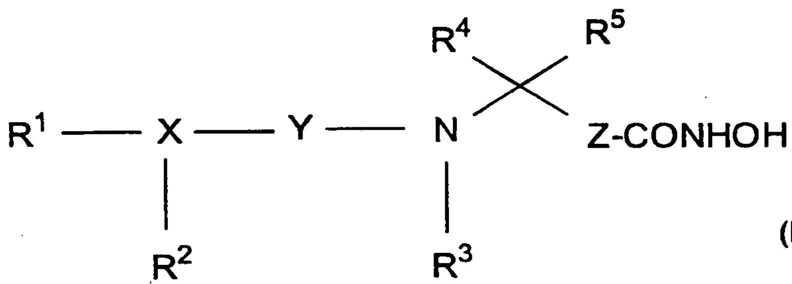


(I-3)

Process 6



(I-4)



(I-3)

In the above formulas (I-1), (I-2), (I-3), (I-4), (II), (III) and (IV), R^1, R^2, R^3, R^4, R^5, R^6, X, Y and Z are as defined above, R^{61} is protected hydroxy, R^7 is imino-protective group, R^8 is protected carboxy, L is a leaving group, m and n are independently an integer of 1 to 5, provided that $2 \leqq m+n \leqq 6$.

The starting compounds (II), (III) and (IV) can be prepared according to the following Preparations or by a conventional method.

Suitable pharmaceutically acceptable salts of the object compounds may be

conventional non-toxic salts and include an acid addition salt such as an organic acid salt (e.g., acetate, trifluoroacetate, maleate, tartrate, fumarate, methanesulfonate, benzenesulfonate, formate, toluenesulfonate, etc.), an inorganic acid salt (e.g., hydrochloride, hydrobromide, hydroiodide, sulfate, nitrate, phosphate, etc.), or a salt with a base such as an amino acid (e.g., arginine, aspartic acid, glutamic acid, etc.), an alkali metal salt (e.g., sodium salt, potassium salt, etc.), an alkaline earth metal salt (e.g., calcium salt, magnesium salt, etc.), an ammonium salt, an organic base salt (e.g., trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, N,N'-dibenzyl-ethylenediamine salt, etc.), or the like.

The object compounds and pharmaceutically acceptable salts thereof may include solvates such as enclosure compounds (e.g., hydrate, etc.).

Suitable examples and illustrations of the various definitions, which the present invention includes within its scope and which are shown in the above and subsequent descriptions of the present specification, are as follows.

Suitable "aryl" in the term "aryl", "optionally substituted aryl", "optionally substituted aryloxy" and "arylthio" includes an aryl having 6 to 10 carbon atoms, such as phenyl, tolyl, xylyl, cumenyl, mesityl, naphthyl and the like, preferably phenyl and naphthyl for R^1, and phenyl for X. Examples of the substituents for substituted aryl are halogen, cyano, nitro, amino, acylamino, lower alkylamino, carbamoyl, hydroxy, lower alkoxy, C_6-C_{10} aryloxy, lower alkyl, C_6-C_{10} aryl, heterocyclic-oxy and the like, preferably heterocyclic-oxy (e.g., pyridyloxy, etc.). Examples of the substituents for substituted aryloxy are the same as ones defined above with regard to "substituted aryl", preferably halogen, lower alkyl and cyano.

Suitable "heterocyclic group" in the term "heterocyclic group", "optionally substituted heterocyclic group" and "heterocyclic-oxy group" means saturated or unsaturated, 3- to 8-membered monocyclic or polycyclic heterocyclic group containing at least one hetero atom such as oxygen atom, sulfur atom, nitrogen atom and the like.

Preferable heterocyclic groups are:

-unsaturated 3- to 8-membered, preferably 5- or 6-membered, heteromonocyclic group containing 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl and its N-oxide, pyrimidyl, pyrazinyl,

pyridazinyl, triazolyl (e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.), tetrazolyl (e.g., 1H-tetrazolyl, 2H-tetrazolyl, etc.), dihydrotriazinyl (e.g., 4,5-dihydro-1,2,4-triazinyl, 2,5-dihydro-1,2,4-triazinyl, etc.), and the like;

-saturated 3- to 8-membered, preferably 5- or 6-membered, heteromonocyclic group containing 1 to 4 nitrogen atoms, for example, azetidinyl, pyrrolidinyl, imidazolidinyl, piperidinyl, piperidino, pyrazolidinyl, piperazinyl, and the like;

-unsaturated condensed, preferably bicyclic, 7- to 13-membered, preferably 9- or 10-membered, heterocyclic group containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, iso-quinolyl, indazolyl, benzotriazolyl, tetrazolopyridyl, tetrazolopyridazinyl (e.g., tetrazolo[1,5-b]pyridazinyl, etc.), dihydrotriazolopyridazinyl, and the like;

-unsaturated 3- to 8-membered, preferably 5- or 6-membered, heteromonocyclic group containing 1 or 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.), and the like;

-saturated 3- to 8-membered, preferably 5- or 6-membered, heteromonocyclic group containing 1 or 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, morpholinyl, morpholino, and the like;

-unsaturated condensed, preferably bicyclic, 7- to 13-membered, preferably 9- or 10-membered, heterocyclic group containing 1 or 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, benzoxazolyl, benzoxadiazolyl, and the like;

-unsaturated 3- to 8-membered, preferably 5- or 6-membered, heteromonocyclic group containing 1 or 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, 1,2-thiazolyl, thiazolinyl, thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,2,3-thiadiazolyl, etc.), and the like;

-saturated 3- to 8-membered, preferably 5- or 6-membered, heteromonocyclic group containing 1 or 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolidinyl, and the like;

-unsaturated 3- to 8-membered, preferably 5- or 6-membered, heteromonocyclic group containing 1 or 2 sulfur atoms, for example, thienyl, and the like;

-unsaturated 3- to 8-membered, preferably 5- or 6-membered, heteromonocyclic group containing 1 or 2 oxygen atoms, for example, furyl, and the like;

-saturated 3- to 8-membered, preferably 5- or 6-membered, heteromonocyclic group containing oxygen atom, for example, oxolanyl, and the like;

-unsaturated condensed, preferably bicyclic, 7- to 13-membered, preferably 9- or 10-membered, heterocyclic group containing 1 or 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, benzothiazolyl, benzothiadiazolyl, and the like;

-unsaturated condensed 7- to 13-membered, preferably 9- or 10-membered, heterocyclic group containing 1 or 2 oxygen atoms, for example, benzodihydrofuranyl, benzodioxolenyl, and the like.

More preferable heterocyclic groups may be unsaturated 5- or 6-membered heteromonocyclic group containing 1 to 4 nitrogen atoms (e.g. pyridyl, etc.), unsaturated 5- or 6-membered heteromonocyclic group containing 1 or 2 sulfur atoms (e.g., thienyl, etc.), unsaturated 5- or 6-membered heteromonocyclic group containing 1 or 2 oxygen atoms (e.g., furyl, etc.), and the most preferable examples are pyridyloxy for R^1 and pyridyl, thienyl and furyl for X.

These heterocyclic groups may have one or more substituents. Examples of the substituents for substituted heterocyclic group are the same as those for optionally substituted aryl or optionally substituted aryloxy.

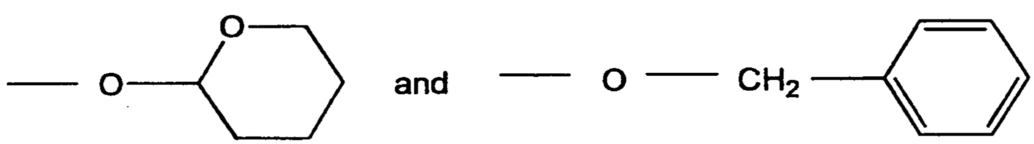
Suitable "aroyl" may include C_6-C_{10} aroyl (e.g., benzoyl, toluoyl, xyloyl, etc.), preferably benzoyl for R^1.

Suitable "lower alkyl" is a straight or branched alkyl having 1 to 6 carbon atoms, and exemplified by methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl and the like, preferably methyl for R^1, and methyl and ethyl for R^4 and/or R^5.

Suitable "lower alkoxy" is a straight or branched alkenyl having 1 to 6 carbon atoms, and exemplified by methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentyloxy, tert-pentyloxy, hexyloxy and the like, preferably methoxy for R^1.

Suitable "protected hydroxy" includes hydroxy protected by a conventional protective group, for example, tetrahydropyranyloxy, substituted lower alkoxy

such as lower alkoxy(lower)alkoxy (e.g., methoxymethoxy), lower alkoxy(lower)alkoxy(lower)alkoxy (e.g., methoxyethoxymethoxy) and substituted or unsubstituted C_6-C_{10} aryl(lower)alkoxy (e.g., benzyloxy, nitrobenzyloxy); acyloxy such as lower alkanoyloxy (e.g., acetoxy, propionyloxy, pivaloyloxy), C_6-C_{10} aroyloxy (e.g., benzoyloxy, fluorenecarbonyloxy), lower alkoxycarbonyloxy (e.g., methoxycarbonyloxy, ethoxycarbonyloxy, propoxycarbonyloxy, isopropoxycarbonyloxy, butoxycarbonyloxy, isobutoxycarbonyloxy, tert-butoxycarbonyloxy, pentyloxycarbonyloxy, hexyloxycarbonyloxy), substituted or unsubstituted C_6-C_{10} aryl(lower)alkoxycarbonyloxy (e.g., benzyloxycarbonyloxy, bromobenzyloxycarbonyloxy), C_6-C_{10} arenesulfonyloxy (e.g., benzenesulfonyloxy, tosyloxy) and alkanesulfonyloxy (e.g., methanesulfonyloxy, ethanesulfonyloxy); tri(lower)alkylsilyloxy (e.g., trimethylsilyloxy); tetrahydropyranyloxy; and the like, preferably, tetrahydropyranyloxy and C_6-C_{10} aryl(lower)alkoxy, and most preferably



The term "lower" is intended to mean 1 to 6 carbon atoms, preferably 1 to 4 carbon atoms, unless otherwise indicated.

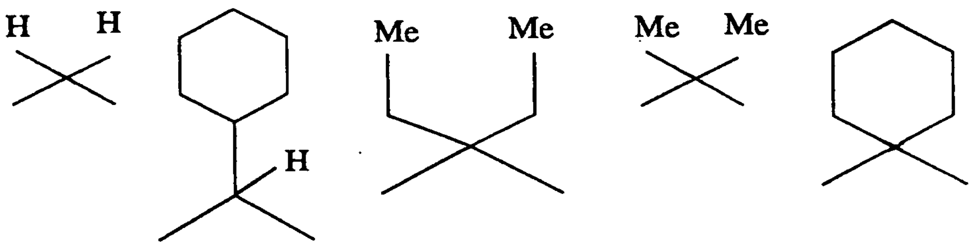
Suitable "halogen" includes fluorine, bromine, chlorine and iodine.

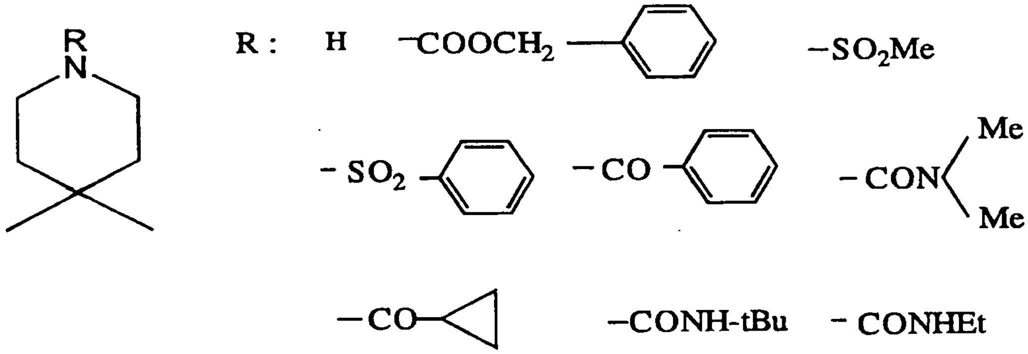
Suitable "lower cycloalkyl" is a cycloalkyl having 3 to 7 carbon atoms, and exemplified by cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, preferably cyclohexyl for R^4 and/or R^5.

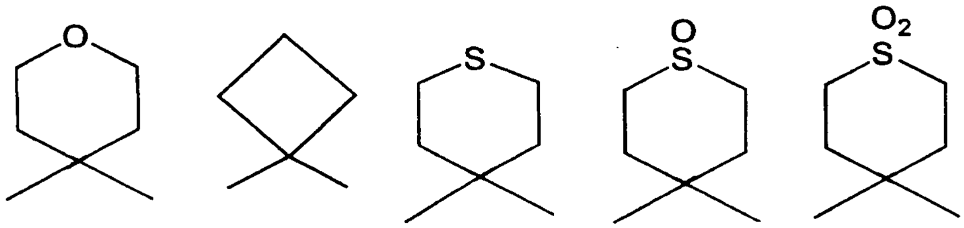
Suitable "lower alkylene" is exemplified by methylene, ethylene, tri-methylene, tetra-methylene, penta-methylene and hexa-methylene, preferably, tri-methylene. tetra-methylene and penta-methylene for R^4 and R^5, methylene and methylmethylene for Z.

Suitable substituent of "optionally mono-substituted nitrogen" is exemplified by C_6-C_{10} ar(lower)alkoxycarbonyl, lower alkylsulfonyl, C_6-C_{10} arylsulfonyl, C_6-C_{10} aroyl, mono- or di(lower)alkylcarbamoyl, lower cycloalkylcarbonyl, and the like.

Suitable R^4 R^5 is exemplified as follows.







Suitable acyl moiety of "acylamino" includes acyl such as aliphatic acyl, aromatic acyl, heterocyclic acyl and aliphatic acyl substituted by aromatic or heterocyclic group(s) derived from carboxylic, carbonic, sulfonic and carbamic acids.

The aliphatic acyl includes saturated or unsaturated, acyclic or cyclic ones, for example, alkanoyl such as lower alkanoyl (e.g., formyl, acetyl, propionyl, butylyl, isobutylyl, valeryl, isovaleryl, pivaloyl, hexanoyl, etc.), alkylsulfonyl such as lower

alkylsulfonyl (e.g., mesyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, butylsulfonyl, isobutylsulfonyl, pentylsulfonyl, hexylsulfonyl, etc.), carbamoyl, N-alkylcarbamoyl (e.g., methylcarbamoyl, ethylcarbamoyl, etc.), alkoxycarbonyl such as lower alkoxycarbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, tert-butoxycarbonyl, etc.), alkenyloxycarbonyl such as lower alkenyloxycarbonyl (e.g., vinyloxycarbonyl, allyloxycarbonyl, etc.), alkenoyl such as lower alkenoyl (e.g., acryloyl, methacryloyl, crotonoyl, etc.), cycloalkanecarbonyl such as cyclo(lower)alkanecarbonyl (e.g., cyclopropanecarbonyl, cyclopentanecarbonyl, cyclohexanecarbonyl, etc.), and the like.

The aromatic acyl may include C_6-C_{10} aroyl (e.g., benzoyl, toluoyl, xyloyl, etc.), N-(C_6-C_{10})arylcarbamoyl (e.g., N-phenylcarbamoyl, N-tolylcarbamoyl, N-naphthylcarbamoyl, etc.), C_6-C_{10} arenesulfonyl (e.g., benzenesulfonyl, tosyl, etc.), and the like.

The heterocyclic acyl may include heterocyclic-carbonyl (e.g., furoyl, thenoyl, nicotinoyl, isonicotinoyl, thiazolylcarbonyl, thiadiazolylcarbonyl, tetrazolylcarbonyl, etc.), and the like.

The aliphatic acyl substituted by aromatic group(s) may include aralkanoyl such as phenyl(lower)alkanoyl (e.g., phenylacetyl, phenylpropionyl, phenylhexanoyl, etc.), aralkoxycarbonyl such as phenyl(lower)alkoxycarbonyl (e.g., benzyloxycarbonyl, phenethyloxycarbonyl, etc.), aryloxyalkanoyl such as phenoxy(lower)alkanoyl (e.g., phenoxyacetyl, phenoxypropionyl, etc.), and the like.

The aliphatic acyl substituted by heterocycic group(s) may include heterocyclic-alkanoyl such as heterocyclic-(lower)alkanoyl (e.g., thienylacetyl, imidazolylacetyl, furylacetyl, tetrazolylacetyl, thiadiazolylpropionyl, etc.), and the like.

Suitable lower alkyl moiety of "lower alkylamino" is the same as lower alkyl defined above.

Suitable compounds having the formula (I) are:

compound (I) wherein

R^1 is halogen, nitro, lower alkoxy, C_6-C_{10} aryloxy optionally substituted by at least one group selected from the group consisting of halogen, cyano, nitro, amino, acylamin, lower alkylamino, carbamoyl, hydroxy, lower alkoxy, C_6-C_{10} aryloxy,

lower alkyl, C_6-C_{10} aryl and heterocyclic-oxy, C_6-C_{10} arylthio, C_6-C_{10} aroyl, heterocyclic-oxy, C_6-C_{10} aryl optionally substituted by at least one group selected from the group consisting of halogen, cyano, nitro, amino, acylamino, lower alkylamino, carbamoyl, hydroxy, lower alkoxy, C_6-C_{10} aryloxy, lower alkyl, C_6-C_{10} aryl and heterocyclic-oxy, or heterocyclic group optionally substituted by at least one group selected from the group consisting of halogen, cyano, nitro, amino, acylamino, lower alkylamino, carbamoyl, hydroxy, lower alkoxy, C_6-C_{10} aryloxy, lower alkyl, C_6-C_{10} aryl and heterocyclic-oxy;

R^4 and R^5 are independently hydrogen, lower alkyl, or lower cycloalkyl, or R^4 and R^5 are combined together to form lower alkylene, which is optionally interrupted by oxygen, sulfur, sulfinyl, sulfonyl or imino, wherein the imino is optionally mono-substituted by a group of C_6-C_{10} ar(lower)alkoxycarbonyl, lower alkylsulfonyl, C_6-C_{10} arylsulfonyl, C_6-C_{10} aroyl, mono(lower)alkylcarbamoyl, di(lower)alkylcarbamoyl or lower cycloalkylcarbonyl;

R^6 is hydroxy, tetrahydropyranyloxy or C_6-C_{10} aryl(lower)alkoxy; and

X is C_6-C_{10} aryl or heterocyclic group,

said heterocyclic group being

unsaturated 3- to 8-membered, heteromonocyclic group containing 1 to 4 nitrogen atoms,

saturated 3- to 8-membered, heteromonocyclic group containing 1 to 4 nitrogen atoms,

unsaturated bicyclic 7- to 13-membered, heterocyclic group containing 1 to 5 nitrogen atoms,

unsaturated 3- to 8-membered, heteromonocyclic group containing 1 or 2 oxygen atoms and 1 to 3 nitrogen atoms,

saturated 3- to 8-membered, heteromonocyclic group containing 1 or 2 oxygen atoms and 1 to 3 nitrogen atoms,

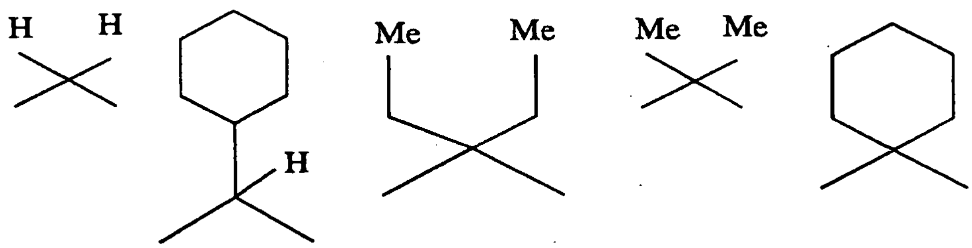
unsaturated bicyclic 7- to 13-membered, heterocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms,

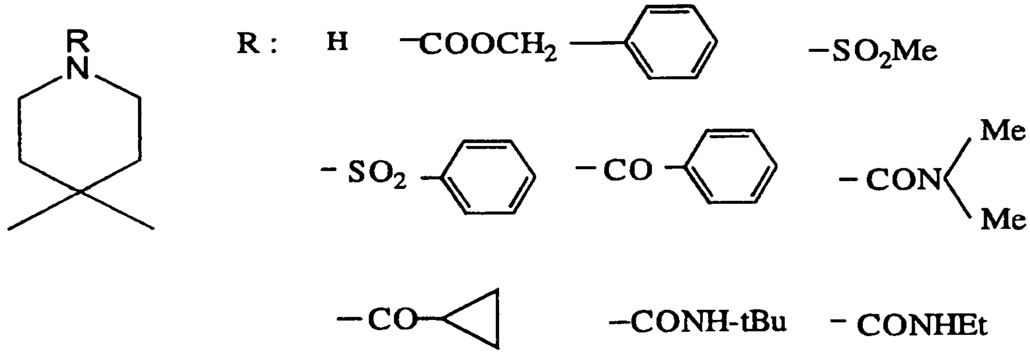
unsaturated 3- to 8-membered, heteromonocyclic group containing 1 or 2 sulfur atoms and 1 to 3 nitrogen atoms,

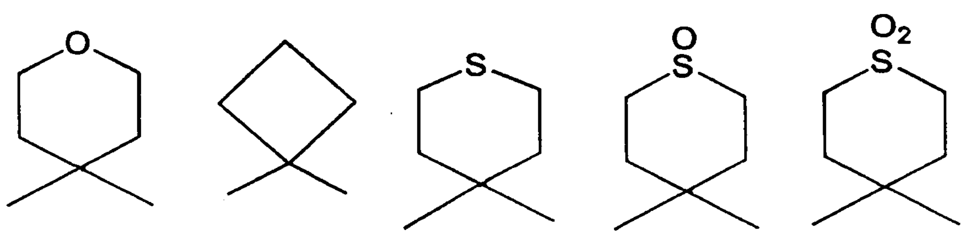
saturated 3- to 8-membered, heteromonocyclic group containing 1 or 2 sulfur atoms and 1 to 3 nitrogen atoms,

unsaturated 3- to 8-membered, heteromonocyclic group containing 1 or 2 sulfur atoms,
unsaturated 3- to 8-membered, heteromonocyclic group containing 1 or 2 oxygen atoms,
saturated 3- to 8-membered, heteromonocyclic group containing oxygen atom,
unsaturated bicyclic 7- to 13-membered, heterocyclic group containing 1 or 2 sulfur atoms and 1 to 3 nitrogen atoms, or
unsaturated bicyclic 7- to 13-membered, heterocyclic group containing 1 or 2 oxygen atoms,
compound (I) wherein
R^1 is halogen; nitro; lower alkoxy; C_6-C_{10} aryloxy optionally substituted by at least one group selected from the group consisting of halogen, cyano, nitro, amino, acylamino, lower alkylamino, carbamoyl, hydroxy, lower alkoxy, C_6-C_{10} aryloxy, lower alkyl, C_6-C_{10} aryl and heterocyclic-oxy, said heterocyclic group being unsaturated 5- or 6-membered, heteromonocyclic group containing 1 to 4 nitrogen atoms; C_6-C_{10} arylthio; C_6-C_{10} aroyl; heterocyclic-oxy, said heterocyclic group being unsaturated 5- or 6-membered, heteromonocyclic group containing 1 to 4 nitrogen atoms; C_6-C_{10} aryl optionally substituted by at least one group selected from the group consisting of halogen, cyano, nitro, amino, acylamino, lower alkylamino, carbamoyl, hydroxy, lower alkoxy, C_6-C_{10} aryloxy, lower alkyl, C_6-C_{10} aryl and heterocyclic-oxy, said heterocyclic group being unsaturated 5- or 6-membered, heteromonocyclic group containing 1 to 4 nitrogen atoms; or heterocyclic group, said heterocyclic group being unsaturated 5- or 6-membered, heteromonocyclic group containing 1 to 4 nitrogen atoms, which is also optionally substituted by at least one group selected from the group consisting of halogen, cyano, nitro, amino, acylamino, lower alkylamino, carbamoyl, hydroxy, lower alkoxy, C_6-C_{10} aryloxy, lower alkyl, C_6-C_{10} aryl and heterocyclic-oxy, said heterocyclic group being unsaturated 5- or 6-membered, heteromonocyclic group containing 1 to 4 nitrogen atoms;
R^4 and R^5 are independently hydrogen, lower alkyl, or lower cycloalkyl, or R^4 and R^5 are combined together to form lower alkylene, which is optionally interrupted by oxygen, sulfur, sulfinyl, sulfonyl, imino, C_6-C_{10} ar(lower)alkoxycarbonylimino, lower alkylsulfonylimino, C_6-C_{10} arylsulfonylimino, C_6-C_{10} aroylimino,

mono(lower)alkylcarbamoylimino, di(lower)alkylcarbamoylimino or lower cycloalkylcarbonylimino, and
X is C_6-C_{10} aryl or heterocyclic group,
said heterocyclic group being
unsaturated 5- or 6-membered, heteromonocyclic group containing 1 to 4 nitrogen atoms, unsaturated 5- or 6-membered, heteromonocyclic group containing 1 or 2 sulfur atoms, or unsaturated 5- or 6-membered, heteromonocyclic group containing 1 or 2 oxygen atoms,
compound (I) wherein
R^1 is halogen; nitro; lower alkoxy; phenoxy or naphthyloxy, each of which is optionally substituted by at least one group selected from the group consisting of halogen, cyano and lower alkyl; phenylthio; benzoly; pyridyloxy; phenyl optionally substituted by halogen; or pyridyl,
R^4 and R^5 are independently hydrogen, lower alkyl, or lower cycloalkyl, or R^4 and R^5 are combined together to form lower alkylene, which is optionally interrupted by oxygen, sulfur, sulfinyl, sulfonyl, imino, phenyl(lower)alkoxycarbonylimino, lower alkylsulfonylimino, phenylsulfonylimino, benzoylimino, mono(lower)alkylcarbamoylimino, di(lower)alkylcarbamoylimino or lower cycloalkylcarbonylimino,
R^6 is hydroxy, tetrahydropyranyloxy or phenyl(lower)alkoxy, and
X is phenyl, pyridyl, thienyl or furyl and
compound (I) wherein
R^1 is halogen; nitro; lower alkoxy; phenoxy, naphthyloxy, halophenoxy, cyanophenoxy, lower alkylphenoxy, phenylthio; benzoyl; pyridyloxy; halophenyl; or pyridyl;
R^4 and R^5 are combined together to form a group of the formula selected from the group consisting of the following formulas:

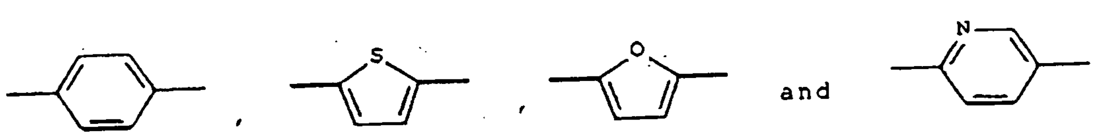






R^6 is hydroxy, and

X is a group selected from the group consisting of



The processes for preparing the object compounds are explained in detail in the following.

Process 1

The compound (I-2) or a salt thereof can be prepared by hydrolysis or reduction of the compound (I-1) or a salt thereof.

Suitable method of this elimination reaction includes conventional ones such as hydrolysis, reduction and the like.

The hydrolysis is preferably carried out in the presence of a base or an acid including Lewis acid.

Suitable base includes an inorganic base and an organic base such as an alkali metal (e.g., sodium, potassium, etc.), an alkaline earth metal (e.g., magnesium, calcium, etc.), the hydroxide or carbonate or hydrogencarbonate thereof, trialkylamine (e.g., trimethylamine, triethylamine, etc.), picoline, 1,5-diazabicyclo[4.3.0]non-5-one, and the like.

Suitable acid includes an organic acid (e.g., formic acid, acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid, etc.), and an inorganic acid (e.g., hydrochloric acid, hydrobromic acid, sulfuric acid, hydrogen chloride, hydrogen bromide, etc.).

The elimination using Lewis acid such as trihaloacetic acid (e.g., trichloroacetic acid, trifluoroacetic acid, etc.) and the like is preferably carried out in the presence of cation trapping agent (e.g., anisole, phenol, etc.). This reaction is usually carried out without solvent.

Alternatively, the reaction may be carried out in a conventional solvent such as water, alcohol (e.g., methanol, ethanol, isopropyl alcohol, etc.), tetrahydrofuran, dioxane, toluene, methylene chloride, ethylene dichloride, chloroform, N,N-dimethylformamide and N,N-dimethylacetamide, a mixture thereof, or any other organic solvents which do not adversely affect the reaction.

The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

The reduction is carried out in a conventional manner, including chemical reduction and catalytic reduction.

Suitable reducing reagents to be used in chemical reduction are a hydride (e.g., hydrogen iodide, hydrogen sulfide, lithium aluminum hydride, sodium borohydride, sodium cyanoborohydride, etc.), or a combination of a metal (e.g., tin, zinc, iron, etc.) or a metallic compound (e.g., chromium chloride, chromium

acetate, etc.) and an organic acid or an inorganic acid (e.g., formic acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid, etc.).

Suitable catalyst to be used in catalytic reduction is conventional one such as platinum catalyst (e.g., platinum plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, platinum wire, etc.), palladium catalyst (e.g., spongy palladium, palladium black, palladium oxide, palladium on carbon, colloidal palladium, palladium on barium sulfate, palladium on barium carbonate, etc.), nickel catalyst (e.g., reduced nickel, nickel oxide, Raney nickel, etc.), cobalt catalyst (e.g., reduced cobalt, Raney cobalt, etc.), iron catalyst (e.g., reduced iron, Raney iron, Ullman iron, etc.), and the like.

The reduction is usually carried out in a conventional solvent such as water, alcohol (e.g., methanol, ethanol, isopropyl alcohol, etc.), tetrahydrofuran, dioxane, toluene, methylene chloride, ethylene dichloride, chloroform, N,N-dimethylformamide, N,N-dimethylacetamide and cyclohexane, a mixture thereof, or any other organic solvents which do not adversely affect the reaction.

When the above-mentioned acids to be used in chemical reduction are liquid, they can also be used as a solvent.

The reaction temperature of this reduction is not critical and the reaction is usually carried out under cooling to warming.

Process 2

The compound (I) or a salt thereof can be prepared by reacting the compound (II) or its reactive derivative at the carboxyl group, or a salt thereof, with the compound: H_2N-R^6 or its reactive derivative at the amino group, or a salt thereof.

Suitable salts of the compound (II) and the compound: H_2N-R^6 may be the same as those exemplified for the compound (I).

The reaction is usually carried out in a conventional solvent such as water, acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethyl-formamide, pyridine and dichloromethane, a mixture thereof, or any other organic solvents which do not adversely affect the reaction.

This reaction can be carried out in the presence of an organic or inorganic base such as alkali metal (e.g., lithium, sodium, potassium, etc.), alkaline earth

metal (e.g., calcium, etc.), alkali metal hydride (e.g., sodium hydride, etc.), alkaline earth metal hydride (e.g., calcium hydride, etc.), alkali metal hydroxide (e.g., sodium hydroxide, potassium hydroxide, etc.), alkali metal carbonate (e.g., sodium carbonate, potassium carbonate, etc.), alkali metal bicarbonate (e.g., sodium bicarbonate, potassium bicarbonate, etc.), alkali metal alkoxide (e.g., sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc.), alkali metal alkanoic acid (e.g., sodium acetate, etc.), trialkylamine (e.g., triethylamine, etc.), pyridine compound (e.g., pyridine, lutidine, picoline, 4-dimethylaminopyridine, etc.), quinoline, lithium diisopropylamide, and the like.

Suitable reactive derivative at the amino group of the compound: H_2N-R^6 may include Schiff's base type imino or its tautomeric enamine type isomer formed by the reaction of the compound: H_2N-R^6 with a carbonyl compound such as aldehyde, ketone or the like; a silyl derivative formed by the reaction of the compound: H_2N-R^6 with a silyl compound such as bis(trimethylsilyl)acetamide, mono(trimethylsilyl)acetamide, bis(trimethylsilyl)urea or the like; a derivative formed by the reaction of the compound: H_2N-R^6 with phosphorus trichloride or phosgene, and the like.

Suitable reactive derivative at the carboxy group of the compound (II) may include an acid halide, an acid anhydride, an activated amide, an activated ester, and the like. Suitable examples of the reactive derivative may be an acid chloride; an acid azide; a mixed acid anhydride with acid such as substituted phosphoric acid (e.g., dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid, etc.), dialkylphosphorous acid, sulfurous acid, thiosulfuric acid, sulfuric acid, sulfonic acid (e.g., methanesulfonic acid, etc.), aliphatic carboxylic acid (e.g., acetic acid, propionic acid, butyric acid, isobutyric acid, pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid, trichloroacetic acid, etc.) or aromatic carboxylic acid (e.g., benzoic acid, etc.); a symmetrical acid anhydride; an activated amide with imidazole, 4-substituted imidazole, dimethylpyrazole, triazole or tetrazole; or an activated ester (e.g., cyanomethyl ester, methoxymethyl ester, dimethyliminomethyl $[(CH_3)_2N^+=CH^-]$ ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenyl azophenyl ester, phenyl

thioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, piperidyl ester, 8-quinolyl thioester, etc.), or an ester with a N-hydroxy compound (e.g., N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)pyridone, N-hydroxysuccinimide, N-hydroxyphthalimide, 1-hydroxy-1H-benzotriazole, etc.), and the like. These reactive derivatives can be optionally selected from them according to the kind of the compound (II) to be used.

The reaction is preferably carried out in the presence of a conventional condensing agent such as N, N'-dicyclohexylcarbodiimide; N-cyclohexyl-N'-morpholinoethylcarbodiimide; N-cyclohexyl-N'-(4-di- ethylaminocyclohexyl)-carbodiimide; N,N'-diethylcarbodiimide; N,N'-di- isopropylcarbodiimide; N-ethyl-N'-(3-dimethylaminopropyl)-carbodiimide; N,N'-carbonylbis-(2-methylimidazole); pentamethyleneketene-N-cyclohexylimine; diphenylketene-N-cyclohexylimine; ethoxyacetylene; 1-alkoxy-1-chloroethylene; trialkyl phosphite; ethyl polyphosphate; isopropyl polyphosphate; phosphorus oxychloride (phosphoryl chloride); phosphorus trichloride; diphenyl phosphorylazide; thionyl chloride; oxalyl chloride; lower alkyl haloformate (e.g., ethyl chloroformate, isopropyl chloroformate); triphenylphosphine; 2-ethyl-7-hydroxybenz- isoxazolium salt; 2-ethyl-5-(m-sulfophenyl)isoxazolium hydroxide intramolecular salt; 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H- benzotriazole; 1-hydroxybenzotriazole; or so-called Vilsmeier reagent prepared by the reaction of N,N-dimethylforamide with thionyl chloride, phosgene, trichloromethyl chloroformate, phosphorus oxychloride or oxalyl chloride.

The reaction temperature is not critical, and the reaction is usually carried out under cooling.

Process 3

The compound (I) or a salt thereof can be prepared by reacting the compound (III) or a salt thereof with the compound: R^1-X(R^2)-Y-L or a salt thereof.

Suitable salts of the compound (III) and the compound: R^1-X(R^2)-Y-L may be the same as those exemplified with respect to the compound (I).

The reaction is usually carried out in a conventional solvent such as water, acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine and

dichloromethane, a mixture thereof, or any other organic solvents which do not adversely affect the reaction.

This reaction can be carried out in the presence of an organic or inorganic base such as alkali metal (e.g., lithium, sodium, potassium, etc.), alkaline earth metal (e.g., calcium, etc.), alkali metal hydride (e.g., sodium hydride, etc.), alkaline earth metal hydride (e.g., calcium hydride, etc.), alkali metal hydroxide (e.g., sodium hydroxide, potassium hydroxide, etc.), alkali metal carbonate (e.g., sodium carbonate, potassium carbonate, etc.), alkali metal bicarbonate (e.g., sodium bicarbonate, potassium bicarbonate, etc.), alkali metal alkoxide (e.g., sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc.), alkali metal alkanoic acid (e.g., sodium acetate, etc.), trialkylamine (e.g., triethylamine, etc.), pyridine compound (e.g., pyridine, lutidine, picoline, 4-dimethylaminopyridine, etc.), quinoline, lithium diisopropylamide, and the like.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to heating.

Process 4

The compound (I-1) or a salt thereof can be prepared by reacting the compound (I-2) or a salt thereof with the compound: R^7-L or lower alkyl isocyanate such as t-butyl-N=C=O, or a salt thereof.

Suitable salts of the compound: R^7-L may be the same as those exemplified for the compound (I).

The reaction of this process can be carried out in a manner similar to that in Process 3.

Process 5

The compound (I-3) or a salt thereof can be prepared by reacting the compound (IV) or a salt thereof with the compound: H_2N-OH or a salt thereof.

Suitable salts of the compound: H_2N-OH may be the same as those exemplified for the compound (I).

The reaction of this process can be carried out in a manner similar to that in Process 2.

Process 6

The compound (I-3) or a salt thereof can be prepared by eliminating the hydroxy protective group of the compound (I-4) or a salt thereof.

The reaction of this process can be carried out in a manner similar to that in Process 1.

The compounds obtained can be isolated and purified by a conventional method such as pulverization, recrystallization, column chromatography, reprecipitation and the like.

The object compounds can be transformed into their salts in a conventional manner.

It is to be noted that the object compounds may include one or more stereoisomers due to asymmetric carbon atoms, and all of such isomers and mixtures thereof are included within the scope of this invention.

Collagenases initiate the degradation of collagen in vertebrates and, in addition to their normal function in the metabolism of connective tissue and wound healing, they have been implicated to be involved in a number of pathological conditions such as joint destruction in rheumatoid arthritis, periodontal disease, corneal ulceration, tumor metastasis, osteoarthritis, decubitus restenosis after percutaneous transluminal coronary angiopsty, osteoporosis, proriasis, chronic active heatitis, autoimmune keratitis, and the like, and therefore the compounds of the present invention are useful for treating and/or preventing such pathological conditions.

Inhibitory activity of MMP can be assayed by a conventional test method as mentioned below.

Test methods:

Test Method 1:

Inhibitory activity of human MMP-1

Human collagenase was prepared from the culture medium of human skin fibroblast stimulated with interleukin-1β (1 ng/ml). Latent collagenase was activated by incubation with tryspin (200 μg/ml) at 37℃ for 60 minutes and the reaction was stopped by adding soybean trypsin inhibitor (800μg/ml). Collagenase activity was determined using FITC-labeled calf skin type I collagen. FITC-collagen (2.5 mg/ml) was incubated at 37℃ for 120 minutes with the activated collagenase and test compound in 50 mM Tris buffer (containing 5 mM $CaCl_2$, 200 mM NaCl and 0.02% NaN_3, pH 7.5). After stopping the enzyme reaction by adding the equal volume of 70% ethanol-200 mM Tris buffer (pH 9.5),

the reaction mixture was centrifuged, and collagenase activity was estimated by measuring the fluorescence intensity of supernatant at 495 nm (excitation) and 520 nm (emission).

Test Method 2:

Inhibitory activity of human MMP-8

The inhibitory activity of test compounds against human MMP-8 were assayed by using commercial kit (Chondrex, USA) contained recombinant human pro-MMP-8 and FITC-labeled telopeptide-free soluble bovine type I collagen as a substrate. Recombinant human pro-MMP-8 was activated by a sequential incubation with mercury compound and proteinase at 35℃ for 1 hour. Reaction mixture containing the activated MMP-8, substrate and test compounds were incubated at 35℃ for 2 hours. After stopping the enzyme reaction by adding the stop solution (o-phenathroline), the reaction mixture was centrifuged and MMP-8 activity was estimated by measuring the fluorescence intensity of supernatant at 490 nm (excitation) and 520 nm (emission).

Test Method 3:

Inhibitory activity of human MMP-9

The inhibitory activity of test compounds against human MMP-9 were measured by using commercial kits (Yagai, Japan). Gelatinolytic activity was determined by monitoring the degradation of FITC-labeled bovine type IV collagen after incubation for 4 hours at 42℃. The amount of degraded collagen was estimated by measuring the fluorescence intensity at 495 nm (excitation) and 520 nm (emission).

Test Method 4:

Inhibitory activity of human MMP-13

The inhibitory potential of test compounds against human MMP-13 were assayed by using commercial kit (Chondrex, USA) contained truncated form of human recombinant MMP-13 and fluorogenic peptide substrate. Activity of human MMP-13 was determined by monitoring the degradation of fluorogenic peptide substrate after incubation for 1 hour at 35℃ and estimated by measuring the fluorescence intensity of degraded peptide substrate at 495 nm (excitation) and 520 nm (emission).

For therapeutic purposes, the compounds and pharmaceutically acceptable

salts thereof of the present invention can be used in the form of a pharmaceutical preparation containing, as an active ingredient, one of said compounds in admixture with a pharmaceutically acceptable carrier such as an organic or inorganic solid or liquid excipient suitable for oral, parenteral or external administration. The pharmaceutical preparations may be capsules, tablets, dragees, granules, solutions, suspensions, emulsions, sublingual tablets, suppositories, ointments, and the like. If desired, there may be included, in these preparations, auxiliary substances, stabilizing agents, wetting agents, emulsifying agents, buffers and other commonly used additives.

While the dose of the compound will vary depending upon the age and condition of patient and the like, in the case of intravenous administration, a daily dose of 0.01 - 100 mg of the active ingredient per kg weight of a human being, and in the case of intramuscular administration, a daily dose of 0.05 - 100 mg of the same per kg weight of a human being, or in the case of oral administration, a daily dose of 0.1 - 100 mg of the same per kg weight of a human being, is generally given for the treatment of MMP or TNFα mediated diseases.

In order to illustrate the usefulness of the object compound, the pharmacological test data of a representative compound of the compound are shown in the following.

Inhibitory activity of human MMP-13

1.Test method

The inhibitory potential of test compounds against human MMP-13 were assayed by using commercial kit (Chondrex, USA) contained truncated form of human recombinant MMP-13 and fluorogenic peptide substrate. Activity of human MMP-13 was determined by monitoring the degradation of fluorogenic peptide substrate after incubation for 1 hour at 35℃ and estimated by measuring the fluorescence intensity of degraded peptide substrate at 495 nm (excitation) and 520 nm (emission).

2. Test Compound

Compound of Example 43

3. Test Result

Test compound	IC_{50} (nM)
Example 43	4.7

Moreover, other abbreviations used in this specification are, for example, as follows.

HOBT: N-Hydroxybenzotriazole

WSCD: N-Ethyl-N'-(3-dimethylaminopropyl)carbodiimide

Bzl: Benzyl

Z: Benzyloxycarbonyl

DMF: Dimethylformamide

The following examples are given for the purpose of illustrating the present invention in detail.

Preparation 1-1

A mixture of cyclohexanone (60.0 g), malonic acid (63.6 g) and sodium acetate (94.2 g) in 95% aqueous ethanol (1 L) was refluxed for 6 days. After cooling to ambient temperature, the resultant mixture was stirred for 6 hours on an ice bath until a solid was formed. The separated solid was collected and washed with ethanol (100 ml) to give 2-(1-aminocyclohexyl)acetic acid (38.3 g).

NMR (D_2O) δ=1.14-1.69(10H, m), 2.38(2H, s)

Mass ESI (-): 156(M-1)

Preparation 1-2

To a solution of 2-(1-aminocyclohexyl)acetic acid (2.0 g) in 1N NaOH (25.4 ml) and dioxane (20 ml) was added Z-Cl (2.17 g) at room temperature. After being stirred for 5 hours, the solution was evaporated in vacuo to remove dioxane. The solution was acidified by 6N HCl and extracted with AcOEt (60 m1). The solution was washed with brine, dried over $MgSO_4$ and concentrated in vacuo to give 2-(1-(benzyloxycarbonylamino)cyclohexyl)acetic acid (1.80 g) as an oil.

NMR ($CDCl_3$) δ=1.18-1.68(8H, m), 1.96-2.20(2H, m), 2.83(2H, s), 4.84(1H, brs), 5.08(2H, s), 732(5H, s)

Mass (ESI-): 290(M-H)

Preparation 1-3

To a solution of 2-(1-(benzyloxycarbonylamino)cyclohexyl)acetic acid (1.5 g), O-(2-tetrahydropyranyl)hydroxylamine (663 mg) and HOBT (765 mg) in DMF (20 ml) was added WSCD · HCl (1.09 g) at room temperature. After being stirred

overnight, the solution was concentrated in vacuo. The residue was dissolved in AcOEt (50 ml) and the solution was washed with 5% aq. citric acid solution, sat. $NaHCO_3$ solution and brine, and dried over $MgSO_4$. The solution was concentrated in vacuo to give N-(2-tetrahydropyranyloxy)-2-(1-(benzyloxy-carbonylamino)cyclohexyl)acetamide (1.83 g) as an amorphous powder.

NMR ($CDCl_3$) δ =1.20-1.91(14H, m), 1.95-2.15(2H, m), 2.60(2H, s), 3.52-3.63(1H, m), 3.80-3.94(1H, m), 4.87(1H, s), 4.90(1H, s), 5.02(1H, d, J=10.5Hz), 5.10(1H, d, J=10.5Hz), 7.35(5H, s), 8.59(1H, s)

Mass (ESI+): 391(M+H)

Preparation 1-4

A solution of N-(2-tetrahydropyranyloxy)-2-(1-(benzyloxycarbonylamino)-cyclohexyl)acetamide (1.8 g) in MeOH (50 ml) was catalytically reduced with 20% palladium hydroxide on carbon (300 mg) under 3 atmospheric pressure of hydrogen for 1 hour. The catalyst was removed by filteration and the filterate was concentrated in vacuo to give N-(2-tetrahydropyranyloxy)-2-(1-aminocyclohexyl)-acetamide (1.18 g) as an oil.

NMR (DMSO-d_6) δ =1.14-1.75(15H, m), 1.95-2.32(3H, m), 3.48-3.59(1H, m), 3.83-3.97(1H, m), 4.34-4.53(2H, m), 5.00-5.10(1H, m)

Mass (ESI+): 257(M+H)

Preparation 2-1

To a solution of thionyl chloride (9.84 g) in MeOH (150 ml) was added 2-(1-aminocyclohexyl)acetic acid (10 g) on an ice-bath. After the mixture was refluxed overnight, it was concentrated in vacuo. The residue was triturated with ether to give methyl 2-(1-aminocyclohexyl)acetate (12.2 g) as a solid.

NMR (DMSO-d_6) δ =1.21-1.52(4H, m), 1.55-1.80(6H, m), 2.77(2H, s), 3.65(3H, s)

Mass (ESI+): 172(M+H)

Preparation 2-2

To a solution of methyl 2-(1-aminocyclohexyl)acetate (500 mg) and N,N-diisopropylethylamine (685 mg) in $CHCl_3$ (10 ml) was added 4-phenoxybenzene-sulfonyl chloride (712 mg) in $CHCl_3$ (5 ml) at room temperature. After stirrring overnight at the same temperature, the reaction mixure was concentrated in vacuo. The residue was dissolved in AcOEt (30 ml) and the solution was washed with 0.5N HCl, sat. $NaHCO_3$ aq, and brine, dried over $MgSO_4$ and concentrated in

vacuo. The residue was crystalized from AcOEt and hexane to give methyl 2-[1-(4-phenoxybenzenesulfonylamino)cyclohexyl]acetate (693 mg).

NMR (DMSO-d_6) δ=1.85-2.02(2H, m), 1.25-1.57(8H, m), 2.60(2H, s), 3.63(3H, s), 5.29(1H, s), 7.01(2H, d, J=8Hz), 7.06(2H, d, J=8Hz), 7.22(1H, t, J=8Hz), 7.41(2H, t, J=8Hz), 7.83(2H, d, J=8Hz)

Mass (ESI-): 402(M-H)

Preparation 2-3

To a solution of methyl 2-[1-(4-phenoxybenzenesulfonylamino)cyclohexyl]-acetate (600 mg) and 60% NaH (65.5 mg) in DMF (10 ml) was added methyl iodide (253 mg) at room temperature. After stirring for 5 hours at the same temperature, the reaction mixture was concentrated in vacuo. The residue was dissolved in AcOEt (30 ml) and the solution was washed with 0.5N HCl, sat. $NaHCO_3$ aq, and brine, dried over $MgSO_4$ and concentrated in vacuo to give methyl 2-[1-N-methyl-N-(4-phenoxybenzenesulfonylamino)cyclohexyl]acetate (580 mg).

NMR ($CDCl_3$) δ=1.30-1.56(6H, m), 1.94-2.12(4H, m), 2.88(3H, s), 2.94(2H, s), 3.66(3H, s), 7.01(2H, d, J=8Hz), 7.06(2H, d, J=8Hz), 7.21(1H, t, J=8Hz), 7.40(2H, t, J=8Hz), 7.80(2H, d, J=8Hz)

Mass (ESI+): 418(M+H)

Preparation 2-4

To a solution of methyl 2-[1-N-methyl-N-(4-phenoxybenzenesulfonylamino)-cyclohexyl]acetate (550 mg) in MeOH (10 ml) was added 1N NaOH aqueous solution (10 ml) at room temperature. After being stirred overnight, the mixture was concentrated in vacuo to remove MeOH. The residual solution was acidified by 1N HCl and extracted with AcOEt (30 ml). The solution was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by SiO_2 column (eluent: $CHCl_3$) to give 2-[1-N-methyl-N-(4-henoxybenzenesulfonyl-amino)cyclohexyl]acetic acid (220 mg) as an oil.

NMR($CDCl_3$) δ=1.27-1.72(6H, m), 1.98-2.12(4H, m), 2.89(3H, s), 3.02(2H, s), 7.01(2H, d, J=8Hz), 7.07(2H, d, J=8Hz), 7.21(1H, t, J=8Hz), 7.41(2H, d, J=8Hz), 7.80(2H, d, J=8Hz)

Mass (ESI-): 402(M-H)

Preparation 3-1

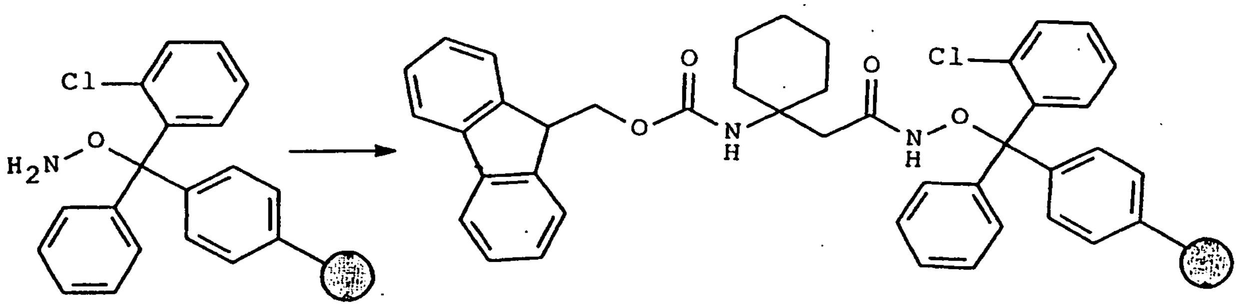
To a solution of 2-(1-aminocyclohexyl)acetic acid (3.5 g) and Na_2CO_3 (4.21 g)

in water (60 ml) was added a solution of 9-fluorenylmethyl succinimidyl carbonate (6.71 g) in dioxane (100 ml) at room temperature. After being stirred for 5 hours, the solution was evaporated in vacuo to remove dioxane. The residue was acidified by 3N HCl and extracted with AcOEt (100 ml X 2). The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The residue was triturated with Et_2O (100 ml) and hexane (100 ml) to give 2-[1-(9-fluorenylmethoxycarbonylamino)cyclohexyl]acetic acid (6.6 g) as a solid.

NMR (DMSO-d_6) δ =1.04-1.62(8H, m), 1.95-2.22(2H, m), 2.57(2H, s), 4.03-4.33(3H, m), 7.04(1H, s), 7.22-7.53(4H, m), 7.73(2H, d, J=8Hz), 7.87(2H, d, J=8Hz)

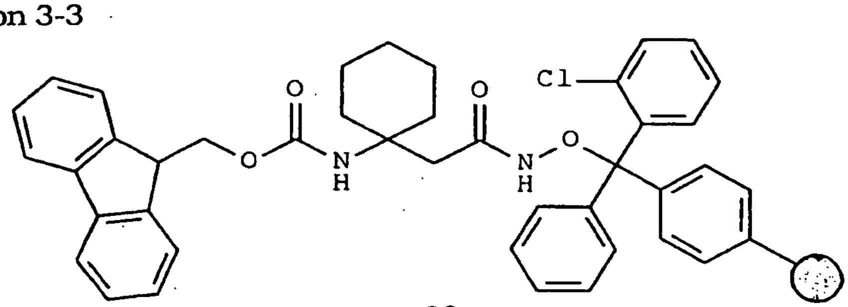
Mass (ESI-): 378(M-H)

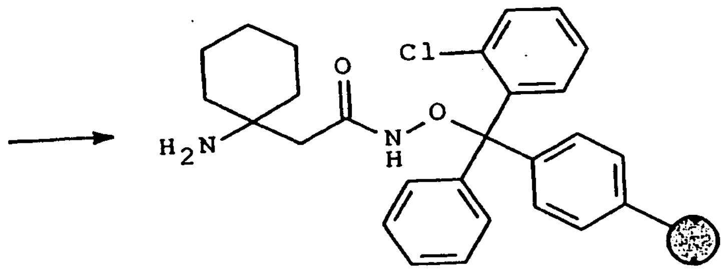
Preparation 3-2



Hydroxylamine 2-chlorotrityl resin (1.46 g) was swelled in N, N-dimethylformamide (10 ml) for 20 minutes. A solution of 2-[1-(9-fluorenylmethoxycarbonylamino)cyclohexyl]acetic acid (2.1 g), O-(7-azabenzotriazol-1-yl)-(1,1,3,3-tetramethyluronium hexafluorophosphate (2.1 g) and N,N-diisopropylethylamine (1.43 g) in N,N-dimethylformamide (10 ml) was added to this suspension and shaken for 24 hours. N-[2-[1-(9-Fluorenylmethoxycarbonylamino)cyclohexyl]-acetyl]hydroxylamine 2-chlorotrityl resin was filtered and washed with N, N-dimethylformamide, methanol and dichloromethane each three times.

Preparation 3-3





N-[2-[1-(9-Fluorenylmethoxycarbonylamino)cyclohexyl]acetyl]-hydroxylamine 2-chlorotrityl resin (2.92 g) was swelled in N, N-dimethylformamide (10 ml) for 20 minutes. To a solution of 20% piperidine in N,N-dimethyl-formamide (20 ml) was added the resin and shaken for 24 hours. N-[2-[1-Aminocyclohexyl]acetyl]hydroxylamine 2-chlorotrityl resin was filtered and washed with N,N-dimethylformamide, methanol and dichloromethane each three times.

Preparation 4-1

To a solution of malonic acid (1.0 g) and ammonium acetate (1.48 g) in EtOH (40 ml) was added tetrahydropyran-4-one (1.01 g) at room temperature. After the reaction solution was stirred at 90℃ for 2 days, it was cooled to room temperature. The resulting precipitate was collected by filteration to give 2-(4-amino-tetrahydropyran-4-yl)acetic acid (450 mg).

NMR (D_2O) δ=1.73(4H, brs), 2.51(2H, s), 3.51-3.58(2H, m), 3.69-3.76(2H, m)

Mass (ESI-): 158(M-H)

Preparation 4-2

2-[4-(Benzyloxycarbonylamino)tetrahydropyran-4-yl]acetic acid was obtained in the similar manner as in Preparation 1-2.

NMR ($CDCl_3$) δ=1.62-1.88(2H, m), 2.08-2.24(2H, m), 2.85(2H, s), 3.47-3.78(4H, m), 4.97(1H, brs), 5.08(2H, s), 7.35(5H, s)

Mass (ESI-): 292(M-H)

Preparation 4-3

N-(2-Tetrahydropyranyloxy)-2-[4-benzyloxycarbonylaminotetrahydropyran-4-yl]acetamide was obtained in the similar manner as in Preparation 1-3.

NMR (DMSO-d_6) δ =1.42-1.73(8H, m), 1.98-2.15(2H, m), 2.39(2H, dd, J=7, 15Hz), 3.40-3.64(6H, m), 3.84-3.96(1H, m), 4.81(1H, s), 5.00(2H, s), 7.15(1H, s), 7.36(5H, s)

Mass (ESI-): 391(M-H)

Preparation 4-4

N-(2-Tetrahydropyranyloxy)-2-(4-aminotetrahydropyran-4-yl)-acetamide was obtained in the similar manner as in Preparation 1-4.

NMR ($CDCl_3$) δ =1.30-1.95(10H, m), 2.35(2H, s), 3.54-3.82(6H, m), 3.88-4.04(1H, m), 4.88-5.07(1H, m)

Mass (ESI+): 259(M+H)

Preparation 5-1

Methyl 2-(4-aminotetrahydropyran-4-yl)acetate hydrochloride (6.18 g) was obtained from 2-(4-aminotetrahydropyran-4-yl)acetic acid (5 g) in the similar manner as in Preparation 2-1 as a solid.

NMR (D_2O) δ =3.77-3.71(2H, m), 3.61-3.53(5H, m), 2.87(2H, s), 1.80(4H, br.s)

ESI(+): 174(M+H)

Preparation 5-2

To a solution of methyl 2-(4-aminotetrahydropyran-4-yl)acetate hydrochloride (1.0 g), 4-phenoxybenzoic acid (1.48 g) and 1-hydroxybenzotriazole (858 mg) in N,N-dimethylformamide (20 ml) was added 1-(3-dimethyl-aminopropyl)-3-ethylcarbodiimide (980 mg) at room temperature. After stirring for 13 hours, the mixture was concentrated in vacuo. The residue was dissolved in AcOEt (100 ml), the solution was washed with 1N HCl, sat. $NaHCO_3$ aq. and brine, dried over $MgSO_4$ and was concentrated in vacuo to give methyl 2-{4-(4-phenoxybenzoylamino)tetrahydropyran-4-yl}acetate (1.0 g) as an amorphous.

NMR ($CDCl_3$) δ =1.78-1.88(2H, m), 2.41-2.46(2H, m), 3.00(2H, s), 3.63(3H, s), 3.68-3.83(4H, m), 6.08(1H, s), 6.99-7.06(4H, m), 7.17(1H, dd, J=7, 7Hz), 7.27-7.41(2H, dd, J=8, 8Hz), 7.73(2H, d, J=9Hz)

ESI(-): 368(M-H)

Preparation 5-3

2-{4-(4-Phenoxybenzoylamino)tetrahydropyran-4-yl}acetic acid (1.0 g) was obtained from methyl 2-{4-(4-phenoxybenzoylamino)tetrahydropyran-4-yl}acetate (1.0 g) in the similar manner as in Preparation 2-4.

NMR (DMSO-D_6) δ =1.62-1.71(2H, m), 2.33-2.38(2H, m), 2.81(2H, s), 3.53-3.67(4H, m), 7.02-7.08(4H, m), 7.20(1H, dd, J=7, 7Hz), 7.41-7.46(2H, dd, J=8, 8Hz), 7.75(2H, d, J=9Hz)

ESI(-): 354(M-H)

Preparation 6-1

2-(4-Aminotetrahydrothiopyran-4-yl)acetic acid was obtained in the similar manner as in Preparation 1.

NMR (D_2O) δ =1.77-1.90(2H, m), 1.95-2.05(2H, m), 2.42(2H, s), 2.49-2.60 (2H, m), 2.61-2.24(2H, m)

Mass ESI(+): 176(M+1)

Preparation 6-2

Methyl 2-(4-aminotetrahydrothiopyran-4-yl)acetate hydrochloride was obtained in the similar manner as in Preparation 2-1.

NMR (DMSO-d_6) δ =1.91-2.10(4H, m), 2.62-2.70(4H, m), 2.73(2H, s), 3.15(3H, s), 8.35(3H, brs., exchangeable)

Mass ESI(+): 190(M+1)

Preparation 6-3

Methyl 2-[4-(4-phenoxybenzenesulfonylamino)tetrahydrothiopyran-4-yl]acetate was obtained in the similar manner as in Example 8 as mentioned below.

NMR ($CDCl_3$) δ =1.75(2H, t, J=12Hz), 2.87(4H, d, J=12Hz), 2.55(2H, s), 2.84(2H, t, J=12Hz), 3.64(3H, s), 5.25(1H, s), 7.04(2H, d, J=8Hz), 7.06(2H, d, J=8Hz), 7.23(1H, t, J=8Hz), 7.42(2H, t, J=8Hz), 7.84(2H, d, J=8Hz)

Mass ESI(-): 420(M-1)

Preparation 6-4

To a solution of methyl 2-[4-(4-phenoxybenzenesulfonylamino)-tetrahydrothiopyran-4-yl]acetate (150 mg) in tetrahydrofuran (2 ml) was added a solution of sodium periodate (76 mg) in water (1 ml) on an ice bath. After been removed the ice bath, the mixture was stirred for 2 days at ambient temperature.

The resultant mixture was extracted with ethyl acetate. The separated organic layer was washed with water and brine, dried over sodium sulfate and evaporated in vacuo. The obtained residue was purified by column chromatography with 1-5% methanol in chloroform stepwise gradient to give methyl 2-[1-oxo-4-(4-phenoxybenzenesulfonylamino)tetrahydrothiopyran-4-yl]-acetate (166 mg) as an amorphous solid.

NMR ($CDCl_3$) δ =2.14-2.31(4H, m), 2.34(2H, s), 2.77(2H, d, J=14Hz), 2.90(2H, td, J=4.5, 14Hz), 3.57(3H, s), 5.52(1H, s), 7.04(2H, d, J=8Hz), 7.07(2H, d, J=8Hz), 7.24(1H, t, J=8Hz), 7.44(2H, t, J=8Hz), 7.80(2H, d, J=8Hz)

Mass ESI(-): 436(M-1)

Preparation 7-1

Methyl 2-[1,1-dioxo-4-(4-phenoxybenzenesulfonylamino)tetrahydro-thiopyran-4-yl]acetate was obtained in the similar manner as in Preparation 6-4.

NMR ($CDCl_3$) δ = 2.08(2H, t, J=13.5Hz), 2.44(2H, s), 2.64(2H, d, J=13.5Hz), 2.84(2H, d, J=13.5Hz), 3.43(3H, t, J=13.5Hz), 3.60(3H, s), 5.50(1H, s), 7.05(2H, d, J=8Hz), 7.80(2H, d, J=8Hz), 7.25(1H, t, J=8Hz), 7.45(2H, t, J=8Hz), 7.81(2H, d, J=8Hz)

Mass ESI(-): 452(M-1)

Preparation 7-2

2-[1,1-Dioxo-4-(4-phenoxybenzenesulfonylamino)tetrahydro-thiopyran-4-yl]acetic acid was obtained in the similar manner as in Preparation 2-4.

NMR (DMSO-d_6) δ =2.03-2.54(6H, m), 2.86-3.05(4H, m), 7.13(4H, d, J=8Hz), 7.25(1H, t, J=8Hz), 7.46(2H, t, J=8Hz), 7.78(1H, s), 7.85(2H, d, J=8Hz), 8.86(1H, s)

Mass ESI(-): 438(M-1)

Preparation 8-1

To a solution of malonic acid (1.0 g) and ammonium acetate (1.48 g) in EtOH (50 ml) was added 1-benzyloxycarbonyl-4-piperidone (2.24 g) at room temperature. After the reaction solution was stirred at 90℃ overnight, the reaction mixture was concentrated in vacuo. The residue was dissolved in 0.5N hydrochloric acid (200 ml) and the solution was washed with ether (200 ml). The aqueous solution was applied to a column of Diaion HP-20 (50 ml) eluting with MeOH (100 ml). After the eluent was concentrated in vacuo, the residue was triturated with ether to give 2-(4-amino-1-benzyloxycarbonylpiperidin-4-yl)acetic acid (1.70 g) as an

amorphous powder.

NMR (DMSO-d_6) δ =1.54-1.65(4H, m), 2.20(2H, s), 3.26-3.42(2H, m), 3.45-3.60(2H, m), 5.08(2H, s), 7.35(5H, s)

Mass (ESI-): 291(M-H)

Preparation 8-2

To a solution of 2-(4-amino-1-benzyloxycarbonylpiperidin-4-yl)acetic acid (1.50 g) in 1N NaOH (7.7 ml) was added a solution of di-tert-butyl dicarbonate (1.68 g) in dioxane (10 ml) at room temperature. After stirring at 40℃ for 6 hours, the mixture was concentrated in vacuo to remove dioxane. The residual solution was acidified with 3N HCl to adjust to pH 2 and extracted with AcOEt (50 ml). The solution was washed with brine, dried over $MgSO_4$ and concentrated in vacuo to give 2-[4-(tert-butoxycarbonylamino)-1-benzyloxycarbonylpiperidin-4-yl]acetic acid (1.48 g) as an amorphous powder.

NMR ($CDCl_3$) δ =1.48(9H, s), 1.50-1.78(2H, m), 2.07-2.32(2H, m), 2.70(2H, brs), 3.03-3.28(2H, m), 3.78-4.02(2H, m), 5.10(2H, s), 7.34(5H, s)

Mass (ESI-): 391(M-H)

Preparation 8-3

To a solution of 2-[4-(tert-butoxycarbonylamino)-1-benzyloxycarbonyl-piperidin-4-yl]acetic acid (1.40 g) and ethyl iodide (668 mg) in DMF (10 ml) was added potassium carbonate (296 mg) at room temperature. After stirring for 4 hours, the reaction solution was concentrated in vacuo. The residue was dissolved in AcOEt (50 ml) and the solution was washed with 1M hydrochloric acid solution, saturated sodium bicarbonate solution and brine, and dried over $MgSO_4$. The solution was concentrated in vacuo to give ethyl 2-[4-(tert-butoxycarbonyl-amino)-1-benzyloxycarbonylpiperidin-4-yl]acetate (1.52 g) as a powder.

NMR ($CDCl_3$) δ =1.25(3H, t, J=7Hz), 1.44(9H, s), 1.48-1.72(2H, m), 2.10-2.31(2H, m), 2.74(2H, s), 3.04-3.30(2H, m), 3.75-3.99(2H, m), 4.12(2H, q, J=7Hz), 4.51(1H, s), 5.12(2H, s), 7.34(5H, s)

Mass (ESI+): 421(M+H)

Preparation 8-4

To a solution of ethyl 2-[4-(tert-butoxycarbonylamino)-1-benzyloxycarbonyl-piperidin-4-yl]acetate (1.48 g) in AcOEt (10 ml) was added 4N hydrogenchloride in AcOEt (20 ml) at room temperature. After stirring for 1 hour, the reaction

solution was concentrated in vacuo. The residue was triturated with ether to give ethyl 2-[4-amino-1-benzyloxycarbonylpiperidin-4-yl]acetate hydrochloride (1.36 g) as a solid.

NMR ($DMSO-d_6$) δ =1.22(3H, t, J=7Hz), 1.70-1.90(4H, m), 2.86(2H, s), 3.30-3.48(2H, m), 3.58-3.76(2H, m), 4.13(2H, q, J=7Hz), 5.08(2H, s), 7.34(5H, s), 8.40(2H, brs)

Mass (ESI+): 321(M+H)

Preparation 8-5

Ethyl 2-[4-(4-phenoxybenzenesulfonylamino)-1-benzyloxycarbonyl-piperidin-4-yl]acetate was obtained in the similar manner as in Example 8 as mentioned below.

NMR ($CDCl_3$) δ =1.23(3H, t, J=7Hz), 1.35-1.53(2H, m), 2.06-2.17(2H, m), 2.48(2H, s), 3.05-3.32(2H, m), 3.62-3.82(2H, m), 4.08(2H, q, J=7Hz), 5.10(2H, s), 5.40(1H, s), 7.02(2H, d, J=8Hz), 7.08(2H, d, J=8Hz), 7.22(1H, t, J=8Hz), 7.33(5H, s), 7.42(2H, t, J=8Hz), 7.81(2H, d, J=8Hz)

Mass (ESI-): 551(M-H)

Preparation 8-6

2-[4-(4-Phenoxybenzenesulfonylamino)-1-benzyloxycarbonyl-piperidin-4-yl]acetic acid (800 mg) was obtained in the same manner as in Preparation 2-4 as an amorphous state.

NMR ($CDCl_3$) δ =1.42-1.60(2H, m), 2.03-2.18(2H, m), 2.65(2H, s), 2.92-3.20(2H, m), 3.62-3.80(2H, m), 5.09(2H, s), 5.58(1H, s), 7.02(2H, d, J=8Hz), 7.06(2H, d, J=8Hz), 7.22(1H, t, J=8Hz), 7.32(5H, s), 7.49(2H, t, J=8Hz), 7.82(2H, d, J=8Hz)

Mass (ESI-): 523(M-H)

Preparation 9-1

2-[1-Benzyloxycarbonyl-4-(9-fluorenylmethoxycarbonylamino)piperidin-4-yl]acetic acid was obtained as an oil from 2-[4-amino-1-benzyloxycarbonyl-piperidin-4-yl]acetic acid in the similar manner as in Preparation 3-1.

NMR ($DMSO-d_6$) δ =1.38-1.63(2H, m), 2.06-2.26(2H, m), 2.62(2H, s), 2.90-3.17(2H, m), 3.62-3.80(2H, m), 4.15-4.32(3H, m), 5.07(2H, s), 7.26-7.48(9H, m), 7.73(2H, d, J=7Hz), 7.88(2H, d, J=7Hz)

Mass (ESI-): 513(M-H)

Preparation 9-2

N-(2-Tetrahydropyranyloxy)-2-[1-benzyloxcarbonyl-4-(9-fluorenylmethoxycarbonylamino)piperidin-4-yl]acetamide was obtained as a powder from 2-[1-benzyloxycarbonyl-4-(9-fluorenylmethoxycarbonylamino)piperidin-4-yl]acetic acid in the similar manner as in Preparation 1-3.

NMR (DMSO-d_6) δ =1.40-1.72(8H, m), 2.08-2.25(2H, m), 2.28-2.49(2H, m), 2.88-3.13(2H, m), 3.36-3.48(2H, m), 3.64-3.78(2H, m), 3.82-3.94(1H, m), 4.78(1H, s), 5.07(2H, s), 7.18-7.48(10H, m), 7.73(2H, d, J=7Hz), 7.89(2H, d, J=7Hz)

Mass (ESI+): 614(M+H)

Preparation 9-3

N-(2-Tetrahydropyranyloxy)-2-[1-benzyloxycarbonyl-4-(9-fluorenylmethoxycarbonylamino)piperidin-4-yl]acetamide (27.5 g) was dissloved in 20% piperidine in DMF (250 ml) at room temperature. After stirring at the same temperature for 1 hour, the solution was concentrated in vacuo. The residue was purified by SiO_2 column chromatography ($CHCl_3$-2% MeOH in $CHCl_3$) to give N-(2-tetrahydropyranyloxy)-2-(4-amino-1-benzyloxycarbonylpiperidin-4-yl)acetamide (15.6 g) as an oil.

NMR (DMSO-d_6) δ =1.22-1.75(10H, mJ=Hz), 2.07(2H, s), 3.35-3.65(6H, m), 3.84-3.96(1H, m), 4.82(1H, s), 5.06(2H, s), 7.27-7.42(5H, m)

Mass (ESI-): 390(M-H)

Preparation 10-1

N-(2-Tetrahydropyranyloxy)-2-benzyloxycarbonylaminopropionamide was obtained as a solid from 2-benzyloxycarbonylaminopropionic acid (5.0 g) in the similar manner as in Preparation 1-3.

NMR (DMSO-d_6) δ =1.42-1.72(6H, m), 2.17(2H, t, J=7Hz), 3.15-3.26(2H, m), 3.45-3.54(1H, m), 3.85-3.95(1H, m), 4.81(1H, s), 5.00(2H, s), 7.25-7.40(5H, m)

Mass (ESI-): 321(M-H)

Preparation 10-2

N-(2-Tetrahydropyranyloxy)-2-aminopropionamide was obtained as an oil from N-(2-tetrahydropyranyloxy)-2-benzyloxycarbonylaminopropionamide in the similar manner as in Preparation 1-4.

NMR (DMSO-d_6) δ =1.20-1.72(6H, m), 2.05-2.30(2H, m), 2.65-2.86(2H, m), 3.32-3.81(2H, m), 4.56-4.82(1H, m)

Mass (ESI+): 189(M+H)

Preparation 11-1

3-Benzyloxycarbonylamino-3-cyclohexylpropionic acid was obtained from 3-amino-3-cyclohexylpropionic acid in the similar manner as in Preparation 1-2.

NMR (DMSO-d_6) δ =0.88-1.43(6H, m), 1.53-1.75(5H, m), 2.18-2.46(2H, m), 3.65-3.79(1H, m), 5.00(2H, s), 7.17(1H, d, J=9Hz), 7.26-7.40(5H, m)

Mass (ESI-): 304(M-H)

Preparation 11-2

N-(2-Tetrahydropyranyloxy)-3-benzyloxycarbonylamino-3-cyclohexyl-propionamide was obtained from 3-benzyloxycarbonylamino-3-cyclohexyl-propionic acid in the similar manner as in Preparation 1-3.

NMR (DMSO-d_6) δ =0.82-1.74(17H, m), 2.00-2.26(2H, m), 3.40-3.53(1H, m), 3.67-3.80(1H, m), 3.84-3.95(1H, m), 4.72-4.81(1H, m), 5.00(2H, s),6.98-7.07(1H, m), 7.26-7.40(5H, m)

Mass (ESI-): 403(M-H)

Preparation 11-3

N-(2-Tetrahydropyranyloxy)-3-amino-3-cyclohexylpropionamide was obtained from N-(2-tetrahydropyranyloxy)-3-benzyloxycarbonylamino-3-cyclohexylpropionamide in the similar manner as in Preparation 1-4.

NMR (DMSO-d_6) δ =0.74-1.76(17H, m), 1.82-2.20(2H, m), 2.71-2.86(1H, m), 3.42-3.57(1H, m), 3.84-4.02(1H, m), 4.74-4.86(1H, m)

Mass (ESI-): 269(M-H)

Preparation 12-1

To a solution of 2-ethyl-1-butene (1.82 g) in Et_2O (8 ml) was added N-chlorosulfonyl isocyanate (3 g) at 0℃ and the mixture was stirred for 5 hours at room temperature. The mixture was poured into water (10 ml) and organic layer was separated. To this ether solution was added an aqueous sodium sulfite solution (9.35 g in 30 ml of water) and the solution was stirred for 1 hour at room temperature. The organic layer was separated, and the aqueous layer was extracted with ether twice. The ether layer was gathered and washed with brine, dried over magnesium sulfate. Solvent was removed under reduced pressure to give 4,4-diethyl-2-azetidinone as a colorless oil.

NMR (DMSO-d_6) δ = 0.93(t, 6H, J=8Hz), 1.70(q, 4H, J=8Hz), 2.64(d, 2H, J=2Hz), 6.14(br, 1H)

MS (ES+)=128.2

Preparation 12-2

To a suspension of sodium hydride (60% oil dispersion, 69 mg) in N,N-dimethylformamide (DMF, 5 ml) was added 4,4-diethyl-2-azetidinone (200 mg) at 0℃, and the mixture was stirred for 30 minutes. Then a solution of 4-phenoxy-benzenesulfonyl chloride (465 mg) in DMF (3 ml) was slowly added at 0℃, and the mixture was stirred for 1 hour at room temperature. The reaction was quenched with 5% aqueous citric acid solution. The organic layer was separated, washed with water (X 2) and brine, and dried over magnesium sulfate. The solvent was evaporated. The oily residue was purified with silica gel column chromatography (eluent: chloroform)to give 1-(4-phenoxy-benzenesulfonyl)-4,4-diethyl-2-azetidinone as a slightly yellow oil.

NMR ($CDCl_3$) δ =0.94(t, 6H, J=7Hz), 1.96(q, 4H, J=7Hz), 2.76 (s, 2H), 7.03-7.09(m, 2H), 7.20-7.26(m, 1H), 7.38-7.45(m, 2H), 7.97(d, 2H, J=9Hz)

Preparation 12-3

To a solution of 1-(4-phenoxybenzenesulfonyl)-4,4-diethyl-2-azetidinone (290 mg) in methanol (5 ml) was added 1N aqueous sodium hydroxide solution (1.2 ml) at room temperature and the mixture was stirred for 5 hours at 50℃. The reaction mixture was cooled to room temperature and acidified with 1N hydrochloric acid (ca. pH=3). This solution was extracted with ethyl acetate (10 ml X 2). The organic layer was combined and washed with water, brine, and dried over magnesium sulfate. The solvent was evaporated. This residue was purified with silica gel column chromatography (eluent: hexane-ethyl acetate 1:1) to give 3-(4-phenoxybenzenesulfonylamino)-3-ethylvaleric acid as a colorless oil.

NMR (DMSO-d_6) δ = 0.66(t, 6H, J=8Hz), 1.53(q, 2H, J=8Hz), 1.64(q, 2H, J=8Hz), 2.36(s, 2H), 7.05-7.13(m, 4H), 7.24(dd, 1H, J=9Hz, 9Hz), 7.46(dd, 2H, J=9Hz, 9Hz), 7.80(d, 2H, J=9Hz)

MS (ES-): 376

Preparation 13-1

t-Butoxycarbonyl dicarbonate (3.43 g) and 4-dimethylaminopyridine (96 mg) were added to a solution of 4,4-diethyl-2-azetidinone (1 g) in acetonitrile (20 ml) at 0℃, and the mixture was stirred overnight. Then, ethyl acetate (25 ml) was added, and the mixture was washed with 1N hydrochloric acid, a saturated solution of

sodium bicarbonate and brine. The organic layer was dried over magnesium sulfate, and the solvent was removed in vacuo. Products were purified by silica gel column chromatography to give 1-(t-butoxycarbonyl)-4,4-diethyl-2-azetidinone as a colorless solid.

NMR ($CDCl_3$) δ=0.95(t, 6H, J=11Hz), 1.52(s, 9H), 1.89(q, 4H, J=11Hz), 2.72 (s, 2H)

Preparation 13-2

To a solution of 1-(t-butoxycarbonyl)-4,4-diethyl-2-azetidinone (300 mg) in methanol (7 ml) was added 1N sodium hydroxide solution (4 ml) at 0℃ and the mixture was stirred for 5 hours at room temperature. The mixture was evaporated to remove methanol. The residue was acidified with 1N hydrochloric acid (ca. pH=3) and extracted with ethyl acetate (X 2). The organic layer was gathered, washed with brine, and dried over magnesium sulfate. The solvent was removed under reduced pressure to give 3-(t-butoxycarbonylamino)-3-ethylvaleric pentanoic acid.

NMR (DMSO-d_6) δ = 0.74(t, 6H, J=8Hz), 1.37(s, 9H), 1.64(q, 4H, J=8Hz), 2.49(s, 2H), 6.23(bs, 1H)

Preparation 13-3

A mixture of 3-(t-butoxycarbonylamino)-3-ethylvaleric acid (315 mg), O-benzylhydroxylamine hydrochloride (307 mg), WSCD (239 mg) and 1-hydroxybenzotriazole (208 mg) in DMF (5 ml) was sttirred at room temperature. After 5 hours, the solvent was evaporated and the residue was partitioned with water (10 ml) and ethyl acetate (10 ml). The organic layer was combined and washed with 5% aqueous citric acid solution, saturated $NaHCO_3$ aq, and brine, and then dried over $MgSO_4$. The solvent was removed under reduced pressure. The crude product was purified with silica gel column chromatography to give N-benzyloxy-3-(t-butoxycarbonylamino)-3-ethylvaleramide.

NMR (DMSO-d_6) δ = 0.84(t, 6H, J=8Hz), 1.40(s, 9H), 1.67(q, 4H, J=8Hz), 2.49(s, 2H), 4.89(s, 2H), 7.33-7.42(m, 5H)

MS (ES-): 349

Preparation 13-4

N-Benzyloxy-3-amino-3-ethylvaleramide hydrochloride was obtained in the similar manner as in Preparation 8-4.

NMR (DMSO-d_6) δ=0.83(t, 6H, J=8Hz), 1.56(q, 4H, J=8Hz), 2.28(s, 2H), 3.38(br, 3H(variable)), 4.84(s, 2H), 7.34-7.44(m, 5H)

MS (ES+): 251

Preparation 14-1

3,4,4-Trimethyl-2-azetidinone was obtained in the similar manner as in Preparation 12-2.

NMR (DMSO-d_6) δ=1.19(d, 3H, J=7Hz), 1.31(s, 3H), 1.42(s, 3H), 1.78(s, 1H), 2.89(q, 1H, J=7Hz)

Preparation 14-2

1-(4-Phenoxybenzenesulfonyl)-3,4,4-trimethyl-2-azetidinone was obtained in the similar manner as in Preparation 12-2.

NMR (DMSO-d_6) δ=1.17(d, 3H, J=7Hz), 1.47(s, 3H), 1.62(s, 3H), 2.98(q, 1H, J=7Hz), 7.02-7.11(m, 4H), 7.24(dd, 1H, J=9Hz, 9Hz), 7.43(dd, 2H, J=9Hz, 9Hz), 7.97(d, 2H, J=9Hz)

Preparation 14-3

2,3-Dimethyl-3-(4-phenoxybenzenesulfonylamino)butyric acid was obtained in the similar manner as in Preparation 12-3.

NMR (DMSO-d_6) δ=1.21(d, 3H, J=7Hz), 1.27(s, 3H), 1.29(s, 3H), 2.66(q, 1H, J=7Hz), 5.81(s, 1H), 6.99-7.09(m, 4H), 7.22(dd, 1H, J=9Hz, 9Hz), 7.41(dd, 2H, J=9Hz, 9Hz), 7.83(d, 2H, J=9Hz)

Preparation 15-1

2-(1-(t-Butoxycarbonylamino)cyclobutyl)acetic acid was obtained in the similar manner as in Preparation 13-2.

NMR ($CDCl_3$) δ=1.45(s, 9H), 1.77-2.02(m, 2H), 2.11-2.31(m, 4H), 2.70-3.03(m, 2H), 5.12(br, 1H)

MS (ES-): 228(M-l)

Preparation 15-2

N-Benzyloxy-2-(1-(t-butoxycarbonylamino)cyclobutyl)acetamide was obtained in the similar manner as in Preparation 1-3.

NMR ($CDCl_3$) δ=1.41(s, 6H), 1.44(s, 3H), 1.75-2.00(m, 2H), 2.10-2.33(m, 4H), 2.65(s, 4/3H), 2.86(s, 2/3H), 4.90(s, 4/3H), 5.04(s, 2/3H), 7.38(s, 5H), 8.33(bs, 1H)

MS (ES-): 333(M-1)

Preparation 15-3

N-Benzyloxy-2-(1-aminocyclobutyl)acetamide was obtained in the similar manner as in Preparation 13-2.

NMR ($CDCl_3$) δ=1.65-1.87(m, 4H), 1.95-2.08(m, 2H), 2.46(s, 2H), 4.92(s, 2H), 7.29-7.43(m, 5H)

MS (ES+)=234(M+1)

Example1

N-(2-Tetrahydropyranyloxy)-2-[4-(4-phenoxybenzenesulfonyl-amino)piperidin-4-yl]acetamide was obtained in the similar manner as in Preparation 1-4.

NMR (DMSO-d_6) δ=1.32-1.90(10H, m), 2.18-2.34(2H, m), 2.47-2.60(2H, m), 3.20-3.54(3H, m), 3.84-3.98(1H, m), 4.80(1H, s), 7.04-7.18(4H, m), 7.20-7.30(1H, m), 7.40-7.52(2H, m), 7.78-7.88(2H, m)

Mass (ESI+): 490(M+H)

Example 2

N-(2-Ttetrahydropyranyloxy)-2-[1-(N-methyl-N-(4-phenoxybenzene-sulfonyl)amino)cyclohexyl]acetamide (250 mg) was obtained from 2-[1-(N-methyl-N-(4-phenoxybenzensulfonyl)amino)cyclohexyl]acetic acid(210 mg) in the similar manner as in Preparation 2-4 as an amorphous powder.

NMR ($CDCl_3$) δ=1.28-2.20(16H, m), 2.70-2.90(2H, m), 2.84(3H, s), 3.59-3.70(1H, m), 3.92-4.06(1H, m), 5.03(1H, s), 7.03(2H, d, J=8Hz), 7.08(2H, d, J=8Hz), 7.22(1H, t, J=8Hz), 7.41(2H, t, J=8Hz), 7.70(2H, d, J=8Hz), 9.13(1H, s)

Mass (ESI+): 503(M+H)

Example 3

N-(2-Tetrahydropyranyloxy)-2-{4-(4-phenoxybenzoylamino)-tetrahydropyran-4-yl}acetamide (1.0 g) was obtained from 2-{4-(4-phenoxybenzoylamino)tetrahydropyran-4-yl}acetic acid (1.0 g) in the similar manner as in Preparation 1-3.

NMR ($CDCl_3$) δ=1.60-1.78(8H, m), 2.32-2.40(2H, m), 2.78-2.88(2H, m), 3.41-3.47(1H, m), 3.67-3.86(4H, m), 6.07(1H, br.s), 6.99-7.07(4H, m), 7.18(1H, dd, J=7, 7Hz), 7.37-7.41(2H, dd, J=8, 8Hz), 7.72 (2H, d, 9Hz)

ESI(-): 453(M-H)

Example 4

N-Tetrahydropyranyloxy-2-[1,1-dioxo-4-(4-phenoxybenzene-sulfonylamino)tetrahydrothiopyran-4-yl]acetamide was obtained in the similar manner as in Preparation 1-3.
NMR ($CDCl_3$) δ=1.49-1.89(6H, m), 2.00-2.21(2H, m), 2.33-2.50(2H, m), 2.52-2.90(4H, m), 3.10-3.30(2H, m), 3.55-3.68(1H, m), 3.80-4.01(1H, m), 4.65(0.5H, s), 4.95(0.5H, s), 5.70(0.5H, s), 6.05(0.5H, s), 7.05(2H, d, J=8Hz), 7.09(2H, d, J=8Hz), 7.25(1H, m), 7.44(2H, t, J=8Hz), 7.80-7.90(2H, m), 8.02(0.5H, s), 8.68(0.5H, s)
Mass ESI(-): 537(M-1)

Example 5

N-(2-Tetrahydropyranyloxy)-2-[4-(4-phenoxybenzenesulfonyl-amino)-1-benzyloxycarbonylpiperidin-4-yl]acetamide was obtained in the similar manner as in Preparation 1-3.
NMR ($CDCl_3$) δ=1.38-2.10(10H, m), 2.33-2.65(2H, m), 2.84-3.26(2H, m), 3.52-3.78(3H, m), 3.92-4.06(1H, m), 5.02(1H, s), 5.08(2H, s), 5.22(1H, s), 7.02(2H, d, J=8Hz), 7.08(2H, d, J=8Hz), 7.24(1H, t, J=8Hz), 7.32(5H, s), 7.83(2H, d, J=8Hz), 8.82(1H, s)
Mass (ESI-): 622(M-H)

Example 6

N-(2-Tetrahydropyranyloxy)-3-(4-phenoxybenzenesulfonylamino)-3-ethylvaler amide was obtained in the similar manner as in Preparation 1-3.
NMR (DMSO-d_6) δ=0.70(t, 3H, J=8Hz), 0.75(t, 3H, J=8Hz), 1.50-1.94(m, 10H), 2.46(dd, 2H, J=7Hz, 16Hz), 3.60-3.70(m, 1H), 4.01(t, 1H, J=10Hz), 5.04(s, 0.5H), 5.18(s, 0.5H), 7.01(d, 2H, J=9Hz), 7.06(d, 2H, J=9Hz), 7.17-7.24(m, 1H), 7.38(dd, 2H, J=9Hz, 9Hz), 7.85(d, 2H, J=9Hz), 8.97(s, 1H)
MS (ES+)=477

Example 7

N-(2-Tetrahydropyranyloxy)-2,3-dimethyl-3-(4-phenoxybenzene-sulfonylamino)butyramide was obtained in the similar manner as in Preparation 1-3.
NMR ($CDCl_3$) δ=1.13-1.31(m, 9H), 1.52-1.93(m, 6H), 2.31(q, 0.5H, J=7Hz), 2.44(q, 0.5H, J=7Hz), 3.63(bs, 1H), 3.67(bs, 1H), 3.90-4.09(m, 1H), 4.99(s, 1H), 5.77(s, 0.5H), 5.93(s, 0.5H), 6.97-7.09(m, 4H), 7.22(dd, 1H, J=9Hz, 9Hz), 7.39(dd, 2H, J=9Hz, 9Hz), 7.83(d, 2H, J=9Hz), 8.66(s, 0.5H), 8.68(s, 0.5H)(diastereomeric

mixture)

MS (ES-)=461

Example 8

To a solution of N-(2-tetrahydropyranyloxy)-2-(1-aminocyclohexyl)acetamide (200 mg) in pyridine (8 ml) was added 4-phenoxybenzenesulfonyl chloride (314 mg) in $CHCl_3$ (4 ml) at room temperature. After being stirred for 4 hours, the solution was concentrated in vacuo. The residue was dissolved in AcOEt (20 ml) and the solution was washed with a 5% aqueous citric acid solution, sat. $NaHCO_3$ solution and brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by SiO_2 column chromatography (eluent: 1% MeOH in $CHCl_3$) to give N-(2-tetrahydropyranyloxy)-2-[1-(4-phenoxybenzenesulfonylamino)cyclohexyl]-acetamide (120 mg) as an amorphous powder.

NMR ($CDCl_3$) δ=1.18-1.95(16H, m), 2.50(1H, d, J=14Hz), 2.53(1H, d, J=14Hz), 3.60-3.70(1H, m), 3.96-4.09(1H, m), 4.98(1H, s), 5.06(1H, s), 7.03(2H, d, J=8Hz), 7.07(2H, d, J=8Hz), 7.22(1H, t, J=8Hz), 7.41(2H, t, J=8Hz), 7.85(2H, d, J=8Hz), 8.95(1H, s)

Mass (ESI-): 487(M-H)

Example 9

N-(2-Tetrahydropyranyloxy)-2-[1-(5-(4-fluorophenyl)thiophen-2-ylsulfonyl-amino)cyclohexyl]acetamide (213 mg) was obtained as an amorphous powder in the similar manner as in Example 8.

NMR ($CDCl_3$) δ=1.22-2.05(16H, m), 2.50(1H, d, J=14Hz), 2.62(1H, d, J=14Hz), 3.51-3.70(1H, m), 3.92-4.08(1H, m), 5.03(1H, s), 5.24(1H, s), 7.03-7.21(3H, m), 7.48-7.65(3H, m), 8.80(1H, s)

Mass (ESI-): 495(M-H)

Example 10

N-(2-Tetrahydropyranyloxy)-2-[1-(4-(4-fluorophenoxy) benzenesulfonyl-amino)cyclohexyl]acetamide was obtained in the similar manner as in Example 8.

NMR ($CDCl_3$) δ=1.24-1.97(16H, m), 2.50(1H, d, J=14Hz), 2.60(1H, d, J=14Hz), 3.95-4.10(1H, m), 5.01(1H, s), 5.04(1H, s), 6.90-7.17(6H, m), 7.28-7.40(1H, m), 7.85(2H, d, J=8Hz), 8.93(1H, s)

Mass (ESI-): 505(M-H)

Example 11

N-(2-Tetrahydropyranyloxy)-2-[1-(4-methoxybenzensulfonylamino)-cyclohexyl]acetamide was obtained as an amorphous powder in the similar manner as in Example 8.

NMR ($CDCl_3$) δ=1.12-2.00(16H, m), 2.42-2.66(2H, m), 3.53(1H, m), 3.87(1H, s), 3.96-4.12(1H, m), 4.90(1H, s), 5.06(1H, s), 6.96(2H, d, J=8Hz), 7.84(2H, d, J=8Hz), 8.98(1H, s)

Mass (ESI-): 425(M-H)

Example 12

N-(2-Tetrahydropyranyloxy)-2-[4-(4-phenoxybenzensulfonylamino)-tetrahydropyran-4-yl]acetamide was obtained in the similar manner as in Example 8.

NMR ($CDCl_3$) δ=1.46-2.02(10H, m), 2.55(2H, dd, J=10, 12Hz), 3.30-3.74(6H, m), 3.95-4.10(1H, m), 5.20(1H, s), 7.02(2H, d, J=8Hz), 7.07(2H, d, J=8Hz), 7.22(1H, t, J=8Hz), 7.40(2H, t, J=8Hz), 7.84(2H, d, J=8Hz), 8.82(1H, s)

Mass (ESI-): 489(M-H)

Example 13

To a solution of N-(2-tetrahydropyranyloxy)-2-(4-amino-1-benzyloxycarbonylpiperidin-4-yl)acetamide (150 mg) in N,N-dimethylformamide (3 ml) was added 1-hydroxybenztriazole (38 mg) and 1-(3-dimethyl-aminopropyl)-3-ethylcarbodiimide (54 mg) at ambient temperature and the reaction mixture was stirred at ambient temperature for 24 hours. The mixture was poured into water and was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium hydrogencarbonate and brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The crude product was purified by column chromatography on silica gel 60 (10 g) using 1% methanol-chloroform to give N-(2-tetrahydropyranyloxy)-2-[1-benzyloxycarbony-4-(4-phenoxybenzoyl-amino)piperidin-4-yl]acetamide as a white amorphous (80 mg).

NMR ($CDCl_3$) δ=1.60(br, 2H), 1.67-1.85(m, 6H), 2.42(br d, J=15Hz, 2H), 2.77(dd, J=12.5, 12.5Hz, 2H), 3.24(br t, J=12.5Hz, 2H), 3.41-3.48(br, 1H), 3.75-3.91(br, 4H), 4.82(s, 1H), 5.13(s, 2H), 6.06(s, 1H), 6.98-7.04(m, 4H), 7.29-7.39(m, 7H), 7.70(d, J=8.0Hz, 2H), 8.50(s, 1H)

MASS (ESI): 586.6 (M-H)

Example 14

N-(2-Tetrahydropyranyloxy)-2-[1-benzyloxycarbonyl-4-(5-(4-fluorophenyl)-thiophen-2-ylcarbonylamino)piperidin-4-yl]acetamide (100 mg) was obtained as a white amorphous from N-(2-tetrahydropyranyl-oxy)-2-(4-amino-1-benzyloxy-carbonylpiperidin-4-yl)acetamide (100 mg) was obtained in the similar manner as in Example 13.

NMR (DMSO-d_6) δ=1.46(br s, 2H), 1.60(br, 6H), 2.40-2.44(m, 2H), 2.53-2.62(m, 2H), 3.15(br, 2H), 3.35-3.43(m, 1H), 3.71-3.76(m, 2H), 3.82-3.90(m, 1H), 4.76(s, 1H), 5.08(s, 2H), 7.25-7.36(m, 6H), 7.51(d, J=3.0Hz, 1H), 7.72-7.77(m, 2H), 7.84(s, 1 H), 7.88(d, J=3.0Hz, 1H)

MASS (ESI): 594.3 (M-H)

Example 15

N-Benzyloxy-3-(4-phenoxybenzoylamino)-3-ethylvaleramide was obtained in the similar manner as in Example 13.

NMR (DMSO-d_6) δ=0.88(t, 6H, J=8Hz), 1.87(q, 2H, J=8Hz), 1.91(q, 2H, J=8Hz), 2.54(s, 2H), 4.84(s, 2H), 6.73(bs, 1H), 6.95-7.08(m, 4H), 7.17(dd, 1H, J=9Hz, 9Hz), 7.27-7.41(m, 7H), 7.71(d, 2H, J=9Hz), 8.62(bs, 1H)

MS (ES-)=445

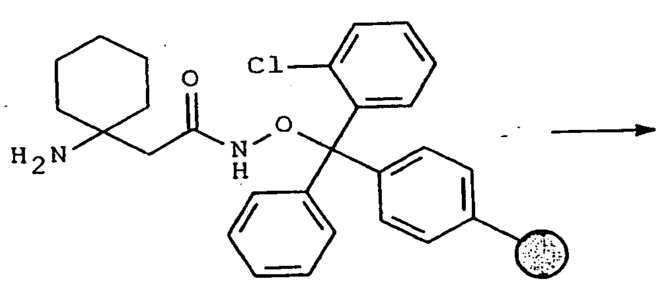
Example 16

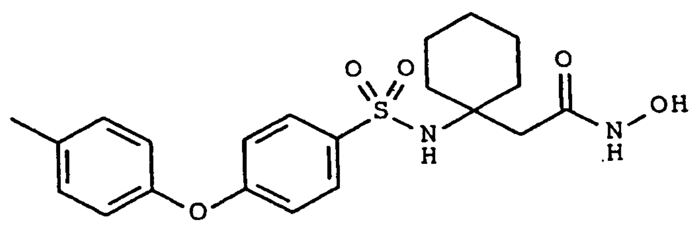
N-Benzyloxy-2-(1-(4-phenoxybenzenesulfonylamino)cyclobutyl)-acetamide was obtained in the similar manner as in Example 8.

NMR ($CDCl_3$) δ=1.52-2.44(m, 6H), 2.60(s, 2H), 4.77(br, 1H), 4.92(s, 1H), 5.50(s, 1H), 6.89-7.49(m, 12H), 7.80(d, 2H, J=8Hz), 8.71(bs, 1H)

MS (ES-): 465(M-l)

Example 17





To a solution of 4-(4-methylphenoxy)benzenesulfonyl chloride (124 mg) and N,N-diisopropylethylamine (57 mg) in dichloromethane (1 ml) was added the N-[2-(1-aminocyclohexyl)acetyl]hydroxylamine 2-chlorotrityl resin (100 mg) and shaken for 24 hours, the resin was filtered and washed successively with 20% piperidine in N,N-dimethylformamide, N,N-dimethylformamide, methanol and dichloromethane each three times. N-[2-[1-{4-(4-Methylphenoxy)benzene-sulfonylamino}cyclohexy]acetyl]hydroxylamine 2-chlorotrityl resin was suspended in a 5% trifluoroacetic acid in dichloromethane for 1 hour. After draining the resin, it was washed successively with a 5% trifluoroacetic acid in dichloromethane and dichloromethane several times. The filtrate was concentrated in vacuo to give N-hydroxy-2-[1-{4-(4-methylphenoxy)benzene-sulfonylamino}cyclohexyl]acetamide as a yellow oil (44 mg).

NMR (DMSO-d_6) δ=1.15-1.29(m, 6H), 1.45-1.52(m, 2H), 1.77-1.82(m, 2H), 2.19(s, 2H), 2.32(s, 3H), 7.00-7.06(m, 4H), 7.26(d, J=8.0Hz, 2H), 7.35(s, 1H), 7.80(d, J=8.0Hz, 2H)

MASS (ESI): 417.2 (M-H)

Example 18

N-Hydroxy-2-[1-(4-phenylthiobenzenesulfonylamino)cyclohexyl]acetamide (40 mg) was obtained as a white amorphous in the similar manner as in Example 17.

NMR (DMSO-d_6) δ=1.11-1.26(m, 6H), 1.41-1.48(m, 2H), 1.73-1.78(m, 2H), 2.17(s, 2H), 7.28(d, J=8.0Hz, 2H), 7.42-7.46(m, 6H), 7.74(d, J=8.0Hz, 2H), 8.79(s, 1H)

MASS (ESI): 421.0 (M-H)

Example 19

N-Hydroxy-2-[1-{4-(4-bromophenoxy)benzenesulfonylamino}-cyclohexyl]acetamide (35 mg) was obtained as a white amorphous in the similar manner as in Example 17.

NMR (DMSO-d_6) δ=1.76-1.93(m, 6H), 2.11(br, 2H), 2.38-2.43(m, 2H), 2.82(s, 2H),

7.78-7.75(m, 4H), 8.02(s, 1H), 8.25(d, J=8.0Hz, 2H), 8.46(d, J=8.0Hz, 2H), 9.44(s, 1H)

MASS (ESI): 483 (M-H)

Example 20

N-Hydroxy-2-[1-(2-phenoxypyridin-5-ylsulfonylamino)cyclohexyl]acetamide was obtained as a yellow oil in the similar manner as in Example 17.

NMR (DMSO-d_6) δ=1.23-1.37(m, 6H), 1.47-1.55(m, 2H), 1.78-1.84(m, 2H), 2.21(s, 2H), 7.20(br d, J=8.0Hz, 2H), 7.27(dd, J=8.0, 8.0Hz, 1H), 7.46(dd, J=8.0, 8.0Hz, 2H), 7.53(br s, 1H), 8.22(br d, J=8.0Hz, 2H), 8.54(br, 1H), 8.80(br, 1H)

MASS (ESI): 404.2 (M-H)

Example 21

N-Hydroxy-2-[1-{4-(4-cyanophenoxy)benzenesulfonylamino}-cyclohexyl]acetamide (78 mg) was obtained as a white amorphous in the similar manner as in Example 17.

NMR (DMSO-d_6) δ=1.29(br, 6H), 1.46-1.54(m, 2H), 1.78-1.85(m, 2H), 2.21(s, 2H), 7.23-7.29(m, 4H), 7.77-7.80(m, 4H), 10.44(s, 1H).

MASS (ESI): 428.1 (M-H)

Example 22

N-Hydroxy-2-[1-(3-fluoro-4-phenoxybenzenesulfonylamino)cyclohexyl]-acetamide (45 mg) was obtained as a white amorphous in the similar manner as in Example 17.

NMR (DMSO-d_6) δ= 1.15-1.32(m, 6H), 1.48-1.56(m, 2H), 1.81-1.86(m, 2H), 2.20(s, 2H), 7.10(d, J=7.0Hz, 2H), 7.10-7.16(m, 2H), 7.42-7.49(m, 3H), 7.65(d, J=8.0Hz, 1H), 7.82(d, J=8.0Hz, 1H), 8.80(s, 1H)

MASS (ESI): 421.1 (M-H)

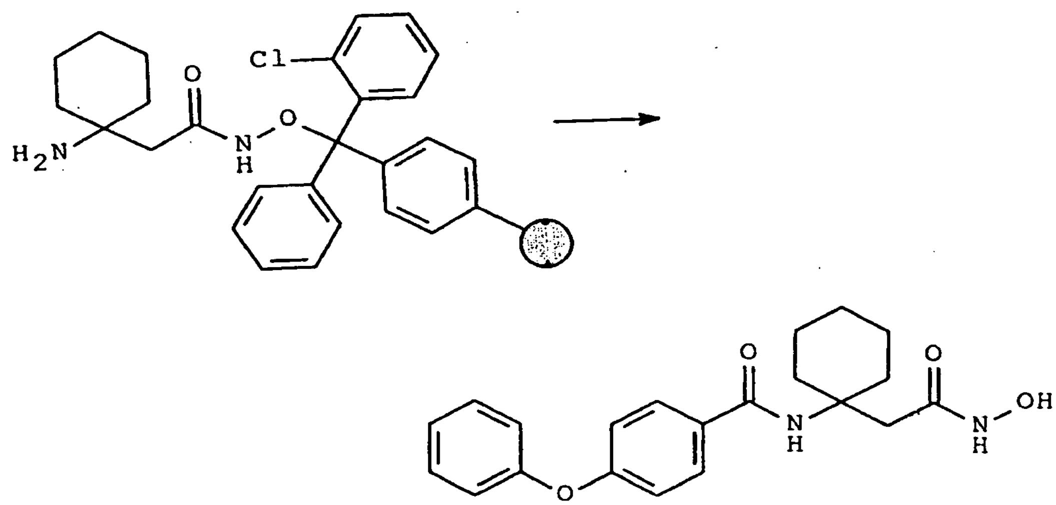
Example 23

N-Hydroxy-2-[1-{4-(naphthalen-2-yloxy)benzenesulfonylamino}-cyclohexyl]acetamide (31 mg) was obtained as a white amorphous in the similar manner as in Example 17.

NMR (DMSO-d_6) δ=1.17-1.31(m, 6H), 1.46-1.54(m, 2H), 1.80-1.86(m, 2H), 2.21(s, 2H), 7.18(d, J=7.0Hz, 2H), 7.30-7.37(m, 2H), 7.46-7.57(m, 3H), 7.83-7.87(m, 3H), 7.95(d, J=7.0Hz, 1H), 8.03(d, J=7.0Hz, 1H), 8.81(s, 1H), 10.44(s, 1H)

MASS (ESI): 453.1 (M-H)

Example 24



To a solution of 4-phenoxybenzoic acid (189 mg) in N,N-dimethyl-formamide (3 ml) were added 1-hydroxybenzotriazole (119 mg) and 1,3-diisopropylcarbodiimide (111 mg) at ambient temperature and the mixture was stirred at ambient temperature for 30 minutes. To the solution was added N-[2-(1-aminocyclohexyl)acetyl]hydroxylamine 2-chlorotrityl resin (200 mg) and shaken for 24 hours. N-[2-{1-(4-phenoxybenzoylamino)cyclohexyl}acetyl]hydroxylamine 2-chlorotrityl resin was filtered and washed with N,N-dimethylformamide, methanol and dichloromethane each three times. The resin was suspended in a 5% trifluoroacetic acid in dichloromethane for 1 hour. After draining the resin, it was washed with a 5% trifluoroacetic acid in dichloromethane and dichloromethane several times. The filtrate was concentrated in vacuo to give N-hydroxy-2-{1-(4-phenoxybenzoylamino)cyclohexyl}acetamide as a white amorphous (84 mg).

NMR (DMSO-d_6) δ=1.23-1.26(m, 2H), 1.46(br, 8H), 2.35-2.39(m, 2H), 7.02-7.08(m, 3H), 7.19(dd, J=7.0, 7.0Hz, 1H), 7.42(dd, J=7.0, 7.0Hz, 2H), 7.73(s, 1H),

7.82(d, J=7.0Hz, 2H), 8.71(s, 1H)
MASS (ESI): 367.2 (M-H)

Example 25

N-Hydroxy-2-[1-(4-phenylthiobenzoylamino)cyclohexyl]acetamide was obtained in the similar manner as in Example 24.

NMR ($CDCl_3$) δ=1.15-2.20(m, 10H), 2.48(d, 2H, J=10Hz), 7.28(d, 2H, J=9Hz), 7.33-7.90(m, 7H), 10.41(bs, 1H)
MS (ES-): 383 (M-H)

Example 26

N-Hydroxy-2-{1-(4-benzoylbenzoylamino)cyclohexyl}acetamide (40 mg) was obtained as a yellow oil in the similar manner as in Example 24.

NMR (DMSO-d_6) δ=1.17-1.63(m, 10H), 2.36(s, 2H), 7.58(dd, J=8.0, 8.0Hz, 1H), 7.68-7.95(m, 8H)
MASS (ESI): 379.2 (M-H)

Example 27

N-Hydroxy-2-[1-{5-(4-chlorophenyl)furan-2-ylcarbonylamino}-cyclohexyl]acetamide (40 mg) was obtained as a white amorphous in the similar manner as in Example 24.

NMR (DMSO-d_6) δ=1.36-1.48(m, 10H), 2.35-2.42(m, 2H), 7.15-7.16(m, 2H), 7.54(d, J=7.5Hz, 2H), 7.91(d, J=7.5Hz, 2H), 7.98(s, 1H)
MASS (ESI): 375.2 (M-H)

Example 28

N-Hydroxy-2-{1-(4-nitrobenzoylamino)cyclohexyl} acetamide (39 mg) was obtained as a white amorphous in the similar manner as in Example 24.

NMR (DMSO-d_6) δ=1.23-1.48(m, 10H), 2.36(br s, 2H), 7.86(br, 1H), 7.99(d, J=7.5Hz, 2H), 8.29(d, J=7.5Hz, 2H), 10.41(br s, 1H)
MASS (ESI): 320.1 (M-H)

Example 29

N-Hydroxy-2-[1-{4-(pyridin-4-yloxy)benzoylamino}cyclohexyl]acetamide (46 mg) was obtained as a yellow oil in the similar manner as in Example 24.

NMR (DMSO-d_6) δ=1.22-1.48(m, 10H), 2.50(br, 2H), 7.36-7.39(m, 4H), 7.88(br s, 2H), 7.97(d, J=7.5Hz, 2H), 8.71(d, J=5.0Hz, 2H), 10.45(s, 1H)
MASS (ESI): 368.2 (M-H)

Example 30

N-Hydroxy-2-[1-(4-bromobenzoylamino)cyclohexyl]acetamide (36 mg) was obtained as a yellow oil in the similar manner as in Example 24.

NMR (DMSO-d_6) δ=1.22(br s, 2H), 1.46(br, 8H), 2.35(br, 2H), 7.65(d, J=7.5Hz, 2H), 7.72(d, J=7.5Hz, 2H), 7.85(br s, 1H)

MASS (ESI): 355.23 (M+H)

Example 31

N-Hydroxy-2-[1-{4-(4-fluorophenoxy)benzoylamino}cyclohexyl]acetamide (38 mg) was obtained as a yellow oil in the similar manner as in Example 24.

NMR (DMSO-d_6) δ=1.23(br s, 2H), 1.46(br, 8H), 2.35-2.47(m, 2H), 7.02(d, J=7.5Hz, 2H), 7.10-7.26(m, 2H), 7.71-7.83(m, 4H), 10.43(s, 1H)

MASS (ESI): 387.2 (M+H)

Example 32

N-Hydroxy-3-(4-phenoxybenzenesulfonylamino)propionamide was obtained from N-(2-tetrahydropyranyloxy)-3-aminopropionamide as a powder in the similar manner as in Example 38 as mentioned below.

NMR (DMSO-d_6) δ=2.14(2H, t, J=7Hz), 2.92(2H, dd, J=7, 8Hz), 7.12(2H, d, J=8Hz), 7.18(2H, d, J=8Hz), 7.26(1H, t, J=8Hz), 7.47(2H, t, J=8Hz), 7.62(1H, t, J=8Hz), 7.78(2H, d, J=8Hz), 8.77(1H, s)

Mass (ESI-): 335(M-H)

Example 33

N-Hydroxy-3-(4-phenoxybenzenesulfonylamino)-3-cyclohexyl-propionamide was obtained from N-(2-tetrahydropyranyloxy)-3-amino-3-cyclohexylpropionamide in the similar manner as in Example 38.

NMR ($CDCl_3$) δ=0.57-1.77(11H, m), 2.19-2.46(2H, m), 3.42-3.59(1H, m), 6.02-6.18(1H, m), 6.90-7.11(4H, m), 7.21(1H, t, J=8Hz), 7.38(2H, t, J=8Hz), 7.82(2H, t, J=8Hz), 9.23(1H, s)

Mass (ESI-): 417(M-H)

Example 34

N-(2-Tetrahydropyranyloxy)-2-[4-(4-phenoxybenzenesulfonyl)-amino-1-methansulfonylpiperidin-4-yl]acetamide was obtained in the similar manner as in Preparation 2-2.

NMR ($CDCl_3$) δ=1.45-1.82(8H, m), 1.98-2.08(2H, m), 2.29(2H, s), 2.64-2.78(2H,

m), 2.75(3H, s), 3.12-3.22(2H, m), 3.45-3.53(1H, m), 3.85-3.96(1H, m), 4.81(1H, s), 7.12(4H, d, J=8Hz), 7.26(1H, t, J=8Hz), 7.47(2H, t, J=8Hz), 7.54(1H, s), 7.85(2H, d, J=8Hz), 8.32(1H, s)

Mass (ESI-): 566(M-H)

Example 35

To a solution of N-(2-tetrahydropyranyloxy)-2-{4-(4-phenoxybenzenesulfonylamino)piperidin-4-yl}acetamide (100 mg) in $CHCl_3$ (2.0 ml) were added Et_3N (20.7 mg) and t-butyl isocyanate (24.3 mg) at room temperature. After being stirred for 10 hours, the solution was concentrated in vacuo. The residue was dissolved in AcOEt and the solution was washed with 1% aqueous citric acid solution, sat. $NaHCO_3$ solution and brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography (eluent: $CHCl_3$) to give N-(2-tetrahydropyranyloxy)-2-{1-(N-t-butylcarbamoyl)-4-(4-phenoxybenzenesulfonylamino)piperidin-4-yl}acetamide (100 mg) as an amorphous.

NMR ($CDCl_3$) δ = 1.26-2.04(19H, m), 2.43-2.57(2H, m), 2.95-3.29 (6H, m), 4.02(1H, dd, J=), 7.01-7.09(4H, m), 7.24(1H, dd, J=7, 7Hz), 7.42(2H, dd, J=8, 8Hz), 7.85(2H, d, J=9Hz)

ESI(-): 587(M-H)

Example 36

To a solution of N-(2-tetrahydropyranyloxy)-2-[4-(4-phenoxybenzenesulfonylamino)piperidin-4-yl]acetamide (150 mg) in 1,2-dichloromethane (4 ml) were added triethylamine (37 mg) and acetylchloride (52 mg) at 0°C and the mixture was stirred at ambient temperature for 24 hours. The reaction mixture was poured into water and was extracted with ethyl acetate. The organic layer was washed with 10% aqueous citric acid solution and brine, dried over anhydrous magnesium sulfate and concentrated in vacuo to give N-(2-tetrahydropyranyloxy)-2-[1-benzoyl-4-(4-phenoxybenzenesulfonylamino)piperidin-4-yl]acetamide as a white amorphous (135 mg).

NMR ($CDCl_3$) δ=1.60(br, 8H), 1.77-1.83(m, 2H), 2.05(s, 2H), 3.43-3.64(m, 2H), 4.00(br, 2H), 5.00(s, 1H), 5.29(s, 1H), 6.00(s, 1H), 7.00-7.09(m, 4H), 7.30-7.44(m, 8H), 7.80-7.88(m, 2H), 8.82(s, 1H)

MASS (ESI): 592.5 (M-H)

Example 37

N-(2-Tetrahydropyranyloxy)-2-[1-(N,N-dimethylcarbamoyl)-4-(4-phenoxybenzenesulfonylamino)piperidin-4-yl]acetamide (160 mg) was obtained from N-(2-tetrahydropyranyloxy)-2-[4-(4-phenoxybenzene-sulfonylamino)piperidin-4-yl]acetamide (140 mg) as a yellow oil in the similar manner as in Example 36.

NMR ($CDCl_3$) δ = 1.61-1.85(m, 8H), 1.92-1.99(m, 2H), 2.42-2.55(m, 3H), 2.77(s, 6H), 2.85-3.00(m, 2H), 3.18-3.27(m, 2H), 3.60-3.66(m, 1H), 3.96-4.04(m, 1H), 7.00-7.08(m, 5H), 7.41(dd, J=7.0, 7.0Hz, 2H), 7.83(d, J=7.0Hz, 2H), 8.92(s, 1H)

MASS (ESI): 559.4 (M-H)

Example 38

To a solution of N-(2-tetrahydropyranyloxy)-2-{4-(4-phenoxybenzene-sulfonylamino)piperidin-4-yl}acetamide (100 mg) in $CHCl_3$ (2.0 ml) were added Et_3N (24.8 mg) and benzenesulfonyl chloride (54.1 mg) at room temperature. After being stirred for 10 hours, the solution was concentrated in vacuo. The residue was dissolved in AcOEt, the solution was washed with 1% aqueous citric acid solution and brine, dried over $MgSO_4$ and concentrated in vacuo.

To a solution of this residue in MeOH (2 ml) was added a 10% HCl in MeOH (1 ml) at room temperature. After being stirred for 1 hour, the solution was concentrated in vacuo. The residue was purified by silica gel column chromatography (10% MeOH in $CHCl_3$) to give N-hydroxy-2- {1-benzenesulfonyl-4-(4-phenoxybenzenesulfonylamino)piperidine-4-yl}acetamide (10 mg) as a power.

NMR ($CDCl_3$) δ =1.55-1.65(4H, m), 2.25-2.39(2H, m), 2.49(2H, br.s), 3.10-3.20(2H, m), 6.86(2H, d, J=8Hz), 7.13(2H, d, J=8Hz), 7.28(1H, dd, J=7, 7Hz), 7.40-7.55(9H, m)

ESI(-): 544(M-H)

Example 39

N-Hydroxy-2-{1-cyclopropylcarbonyl-4-(4-phenoxybenzenesulfonylamino)-piperidin-4-yl}acetamide (10 mg) was obtained from N-(2-tetrahydropyranyloxy)-2-{4-(4-phenoxybenzenesulfonylamino)piperidin-4-yl}acetamide (100 mg) in the similar manner as in Example 38.

NMR ($CDCl_3$) δ =0.69-0.71(2H, m), 0.89-0.91(2H, m), 1.59-1.79(5H, m), 2.2(1H, br.s), 2.52(1H, br.s), 2.65-2.71(2H, m), 3.70-3.82(2H, m), 6.37(1H, br.s), 6.99-7.09(4H, m), 7.21(1H, dd, J=7, 7Hz), 7.42(2H, dd, J=8, 8Hz), 7.83(2H, d, J=9Hz)

ESI(-): 472(M-H)

Example 40

To a solution of N-(2-tetrahydropyranyloxy)-2-{4-(4-phenoxybenzene-sulfonylamino)piperidin-4-yl}acetamide (100 mg) in $CHCl_3$ (2.0 ml) was added Et_3N (20.7 mg) and ethyl isocyanate (17.4 mg) at room temperature. After being stirred for 10 hours, the solution was concentrated in vacuo. The residue was dissolved in AcOEt and the solution was washed with 1% aqueous citric acid solution and brine, dried over $MgSO_4$ and concentrated in vacuo.

To a solution of this residue in MeOH (2 ml) was added a 10% HCl in MeOH (1 ml) at room temperature. After being stirred for 1 hour, the solution was concentrated in vacuo. The residue was purified by silica gel column chromatography (10% MeOH in $CHCl_3$) to give N-hydroxy-2- {1-(N-ethyl-carbamoyl)-4-(4-phenoxybenzenesulfonylamino)piperidin-4-yl}acetamide (13.6 mg) as a power.

NMR ($CDCl_3$) δ=1.07(3H, dd, J=7.5, 7.5Hz), 1.55-1.65(4H, m), 2.59(2H, br.s), 2.86-2.94(2H, m), 3.16-3.20(2H, m), 3.32-3.37(2H, m), 6.96-7.07(4H, m), 7.21(1H, dd, J=7, 7Hz), 7.40(2H, dd, J=8, 8Hz), 7.81(2H, d, J=9Hz)

ESI(-): 472(M-H)

Example 41

A solution of hydroxylamine in methanol (1.7 M, 1.1 ml) prepared as described in Fieser and Fieser, Vol 1, p 478) was added to a solution of methyl 2-[4-(4-phenoxybenzenesulfonylamino)tetrahydrothiopyran-4-yl]acetate (100 mg) at ambient temperature. After stirring for 5 hours, the mixture was acidified with 1N hydrochloric acid and concentrated. The residue was extracted with ethyl acetate. The separated organic phase was washed with brine, dried over sodium sulfate and evaporated in vacuo. The obteined oil was purified by preparative thin layer chromatography with 10% methanol in chloroform and triturated with diisopropyl ether to give N-hydroxy-2-[4-(4-phenoxybenzenesulfonylamino)-tetrahydrothiopyran-4-yl]acetamide (16 mg) as a powder.

NMR (DMSO-d_6) δ=1.84(2H, t, J=12Hz), 2.05-2.23(4H, m), 2.76-2.91(2H, m), 2.63(2H, t, J=12Hz), 7.12(4H, d, J=8Hz), 7.25(1H, t, J=8Hz), 7.40-7.53(3H, m), 7.85(2H, d, J=8Hz), 8.85(1H, s)

Mass ESI(-): 421(M-1)

Example 42

N-Hydroxy-2-[1-oxo-4-(4-phenoxybenzenesulfonylamino)tetrahydrothiopyran-4-yl]acetamide was obtained in the similar manner as in Example 41.

NMR (DMSO-d_6) δ =1.89-2.40(5H, m), 2.40-2.70(1H, m), 2.90-3.05(4H, m), 7.14(4H, d, J=8Hz), 7.25(1H, t, J=8Hz), 7.47(2H, t, J=8Hz), 7.77(1H, s), 7.85(2H, d, J=8Hz), 8.86(1H, s)

Mass ESI(-): 437(M-1)

Example 43

To a solution of N-(2-tetrahydropyranyloxy)-2-[1-(4-phenoxybenzenesulfonylamino)cyclohexyl]acetamide (120 mg) in MeOH (4 ml) was added 10% HCl in MeOH (1 ml) at room temperature. After being stirred for 30 minutes, the solution was concentrated in vacuo. The residue was purified by SiO_2 column chromatography (eluent: 1% MeOH in $CHCl_3$) to give N-hydroxy-2-[1-(4-phenoxybenzenesulfonylamino)cyclohexyl]acetamide (80 mg) as an amotphous powder.

NMR ($CDCl_3$) δ =0.98-1.96(10H, m), 2.56(2H, s), 6.14(1H, s), 7.00(2H, d, J=8Hz), 7.05(2H, d, J=8Hz), 7.22(1H, t, J=8Hz), 7.40(2H, d, J=8Hz), 7.85(2H, d, J=8Hz), 8.98(1H, s)

Mass (ESI+): 405(M+H)

Example44

N-Hydroxy-2-[1-(5-(4-fluorophenyl)thiophen-2-ylsulfonylamino)cyclohexyl]-acetamide (68 mg) was obtained as an amotphous powder in the similar manner as in Example 43.

NMR ($CDCl_3$ DMSO-d_6) δ =1.15-2.05(10H, m), 2.58(2H, s), 6.17(1H, s), 7.00-7.19(3H, m), 7.47-7.63(3H, m), 8.80(1H, s)

Mass (ESI-): 391(M+H)

Example 45

N-Hydroxy-2-[1-(4-(4-fluorophenoxy)benzenesulfonylamino)cyclohexyl]-acetamide was obtained in the similar manner as in Example 43.

NMR ($CDCl_3$) δ =1.16-1.42(6H, m), 1.48-1.90(4H, m), 2.56(2H, s), 6.00(1H, s), 6.89-7.18(6H, m), 7.84(2H, d, J=8Hz), 8.86(1H, brs)

Mass (ESI-): 421(M-H)

Example 46

N-Hydroxy-2-[1-(4-methoxybenzensulfonylamino)cyclohexyl]acetamide (120

mg) was obtained as an amorphous powder in the similar manner as in Example 43.

NMR ($CDCl_3$) δ=1.02-1.68(8H, m), 1.65-1.90(2H, m), 2.17(2H, s), 3.82(3H, s), 7.08(2H, d, J=8Hz), 7.28(1H, s), 7.76(2H, d, J=8Hz), 8.82(1H, s), 10.4(1H, s)

Mass (ESI-): 341 (M-H)

Example 47

N-Hydroxy-2-[1-N-methyl-N-(4-phenoxybenzenesulfonylamino)cyclohexyl]-acetamide (160 mg) was obtained as an amorphous powder in the similar manner as in Example 43.

NMR ($CDCl_3$) δ=1.30-1.64(6H, m), 1.96-2.14(4H, m), 2.78(3H, s), 2.82(2H, s), 7.03(2H, d, J=8Hz), 7.07(2H, d, J=8Hz), 7.23(1H, t, J=8Hz), 7.42(2H, t, J=8Hz), 7.79(2H, d, J=8Hz), 9.28(1H, s)

Mass (ESI+): 419(M+H)

Example 48

N-Hydroxy-2-[4-(4-phenoxybenzenesulfonylamino)tetrahydropyran-4-yl]-acetamide was obtained in the similar manner as in Example 43.

NMR (DMSO-d_6) δ=1.60-1.95(4H, m), 2.25(2H, s), 3.20-3.55(4H, m), 7.10(2H, d, J=8Hz), 7.14(2H, d, J=8Hz), 7.25(1H, t, J=8Hz), 7.48(2H, t, J=8Hz), 7.54(1H, s), 7.83(2H, d, J=8Hz), 10.4(1H, s)

Mass (ESI-): 405(M-H)

Example 49

N-Hydroxy-2-{4-(4-phenoxybenzoylamino)tetrahydropyran-4-yl}-acetamide (0.40 g) was obtained in the similar manner as in Example 43.

NMR (DMSO-d_6) δ=1.61-1.71(2H, m), 2.36-2.40(2H, m), 2.54(2H, s), 3.55-3.65(4H, m), 7.02-7.08(4H, m), 7.20(1H, dd, J=7, 7Hz), 7.43(2H, dd, J=8, 8Hz), 7.85(2H, d, J=9Hz), 8.69(1H, s)

ESI(-): 369(M-H)

Example 50

N-Hydroxy-2-[1,1-dioxo-4-(4-phenoxybenzenesulfonylamino)tetrahydro-thiopyran-4-yl]acetamide was obtained in the similar manner as in Example 43.

NMR (DMSO-d_6) δ=2.14-2.40(6H, m), 2.90-3.06(4H, m), 7.15(4H, d, J=8Hz), 7.25(1H, t, J=8Hz), 7.46(2H, t, J=8Hz), 7.79(1H, s), 7.86(2H, d, J=8Hz) 8.87(1H, s)

Mass ESI(-): 453(M-1)

Example 51

N-Hydroxy-2-[4-(4-phenoxybenzenesulfonylamino)-1-benzyloxycarbonyl-piperidin-4-yl]acetamide was obtained in the similar manner as in Example 43.

NMR ($CDCl_3$) δ=1.46-1.72(2H, m), 1.89-2.17(2H, m), 2.40-3.06(4H, m), 3.44-3.67(2H, m), 5.04(2H, s), 6.28(1H, s), 6.97(2H, d, J=8Hz), 7.05(2H, d, J=8Hz), 7.15-7.47(8H, m), 7.80(2H, d, J=8Hz), 8.98(1H, s)

Mass (ESI-): 538(M-H)

Example 52

N-Hydroxy-2-[4-(4-phenoxyphenylsulfonylamino)piperidin-4-yl]acetamide hydrochloride was obtained in the similar manner as in Example 43.

NMR ($CDCl_3$ DMSO-d_6) δ=1.78-2.28(6H, m), 2.67-2.90(2H, m), 2.95-3.12(2H, m), 7.12(2H, d, J=8Hz), 7.14(2H, d, J=8Hz), 7.28(1H, t, J=8Hz), 7.47(2H, t, J=8Hz), 7.85(2H, d, J=8Hz), 8.48-8.64(1H, m), 8.88-9.00(1H, m)

Mass (ESI+) : 406(M+H)

Example 53

N-Hydroxy-2-[4-(4-phenoxybenzenesulfonylamino)-1-methansulfonyl-piperidin-4-yl]acetamide was obtained in the similar manner as in Example 43.

NMR (DMSO-d_6) δ=1.70-1.85(2H, m), 1.96-2.08(2H, m), 2.24(2H, s), 2.65-2.80(2H, m), 2.76(3H, s), 3.12-3.24(2H, m), 7.12(4H, d, J=8Hz), 7.26(1H, t, J=8Hz), 7.47(2H, t, J=8Hz), 7.58(1H, s), 7.84(2H, d, J=8Hz)

Mass (ESI-): 482(M-H)

Example 54

N-Hydroxy-2-{1-(N-t-butylcarbamoyl)-4-(4-phenoxybenzene-sulfonylamino)piperidin-4-yl}acetamide (14.7 mg) was obtained in the similar manner as in Example 43.

NMR ($CDCl_3$) δ=1.26-1.72(13H, m), 2.80-2.97(2H, m), 3.06-3.18(2H, m), 3.29-3.43(2H, m), 6.96-7.07(4H, m), 7.21(1H, dd, J=7, 7Hz), 7.41(2H, dd, J=8, 8Hz), 7.79(2H, d, J=9Hz)

ESI(-): 503(M-H)

Example 55

N-Hydroxy-2-[1-benzoyl-4-(4-phenoxybenzenesulfonylamino)piperidin-4-yl]acetamide (65 mg) was obtained as white crystals in the similar manner as in Example 43.

NMR (DMSO-d_6) δ=1.63-1.71(m, 2H), 1.83-1.97(m, 2H), 2.26(s, 2H), 2.88(br, 2H), 3.03(br, 2H), 7.10 (d, J=8.0Hz, 3H), 7.22-7.30(m, 3H), 7.40-7.48(m, 5H), 7.62(s, 1H), 7.84(d, J=8.0Hz, 2H), 8.80(s, 1H), 10.43(s, 1H)

MASS (ESI): 508.3 (M-H)

Example 56

N-Hydroxy-2-[1-(N,N-dimethylcarbamoyl)-4-(4-phenoxybenzenesulfonylamino)piperidin-4-yl]acetamide (75 mg) was obtained as a white powder in the similar manner as in Example 43.

NMR (DMSO-d_6) δ=1.62(t, J=9.0Hz, 2H), 1.87(br d, J=9.0Hz, 2H), 2.23(s, 2H), 2.66(s, 6H), 2.75(t, J=9.0Hz, 2H), 3.11(br d, J=9.0Hz, 3H), 7.11(d, J=8.0Hz, 3H), 7.24(dd, J=7.0, 7.0Hz, 1H), 7.42-7.51(m, 3H), 7.83(d, J=8.0Hz, 2H), 8.80(s, 1H)

MASS (ESI): 475.3 (M-H)

Example 57

N-Hydroxy-2-[1-benzyloxycarbonyl-4-(4-phenoxybenzoylamino)piperidin-4-yl]acetamide (40 mg) was obtained as a white amorphous in the similar manner as in Example 43.

NMR (DMSO-d_6) δ=1.53-1.63(m, 2H), 2.42(br, 2H), 2.51(s, 2H), 3.07-3.20(br, 2H), 3.69-3.74(m, 2H), 5.07(s, 2H), 6.98-7.09(m, 4H), 7.30-7.46(m, 7H), 7.83-7.86(m, 2H), 8.70(s, 1H)

MASS (ESI): 502.4 (M-H)

Example 58

N-Hydroxy-2-[1-benzyloxycarbonyl-4-(5-(4-fluorophenyl)thiophen-2-ylcarbonylamino)piperidin-4-yl]acetamide (55 mg) was obtained as a white amorphous in the similar manner as in Example 43.

NMR (DMSO-d_6) δ=1.56-1.65(m, 2H), 2.40-2.46(m, 2H), 2.53(s, 2H), 3.15(br, 2H), 3.70-3.76(m, 2H), 5.08(s, 2H), 7.26-7.36(m, 5H), 7.51(d, J=3.0Hz, 1H), 7.72-7.77(m, 2H), 7.89(m, 2H), 8.72(s, 1H), 10.43(s, 1H)

MASS (ESI): 510.2 (M-H)

Example 59

N-Hydroxy-3-(4-phenoxybenzenesulfonylamino)-3-ethylvaleramide was obtained in the similar manner as in Example 43.

NMR (DMSO-d_6) δ = 0.69(t, 6H, J=8Hz), 1.46-1.70(m, 4H), 2.15(s, 2H), 7.05-7.14(m, 4H), 7.24(dd, 1H, J=9Hz, 9Hz), 7.46(dd, 2H, J=9Hz, 9Hz), 7.81(d, 2H,

J=9Hz)

MS (ES-): 391

Example 60

N-Hydroxy-2,3-dimethyl-3-(4-phenoxybenzenesulfonylamino)butyramide was obtained in the similar manner as in Example 43.

NMR ($CDCl_3$) δ=0.98(d, 3H, J=7Hz), 1.08(s, 3H), 1.20(s, 3H), 2.25(q, 1H), 7.06-7.15(m, 4H), 7.25(dd, 1H, J=9Hz, 9Hz), 7.47(dd, 2H, J=9Hz, 9Hz), 7.81(d, 2H, J=9Hz), 8.86(s, 1H)

MS (ES-): 377

Example 61

To a solution of N-benzyloxy-3-(4-phenoxybenzoylamino)-3-ethylvaleramide (69 mg) was added palladium on carbon (10 mg) and shaken vigorously under hydrogen atmosphere (3 atm.). After 3 hours, the catalyst was removed by filtration and the solvent was removed under reduced pressure. The crude product was purified with silica gel column chromatography (eluent: 1% methanol in chloroform) to give N-hydroxy-3-(4-phenoxybenzoylamino)-3-ethylvaleramide.

NMR (DMSO-d_6) δ=0.69(t, 6H, J=8Hz), 1.46-1.70(m, 4H), 2.15 (s, 2H), 7.05-7.14(m, 4H), 7.24(dd, 1H, J=9Hz, 9Hz), 7.46(dd, 2H, J=9Hz, 9Hz), 7.81(d, 2H, J=9Hz)

MS (ES-): 445

Example 62

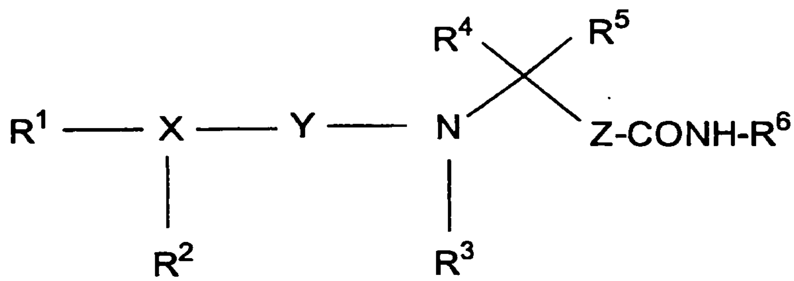
N-Hydroxy-2-(1-(4-phenoxybenzenesulfonylamino)cyclobutyl)acetamide was obtained in the similar manner as in Example 61.

NMR (DMSO-d_6) δ=1.48-1.65(m, 2H), 1.90-2.04(m, 2H), 2.06-2.20(m, 2H), 2.35(s, 2H), 7.10(d, 2H, J=8Hz), 7.14(d, 2H, J=8Hz), 7.25(t, 1H, J=8Hz), 7.47(t, 2H, J=8Hz), 7.75(s, 1H), 7.83(d, 2H, J=8Hz), 8.83(s, 1H), 10.43(s, 1H)

MS (ES-): 375(M-1)

CLAIMS

1. A compound of the formula (I):



(I)

wherein

R^1 is halogen, nitro, lower alkoxy, optionally substituted aryloxy, arylthio, aroyl, heterocyclic-oxy, optionally substituted aryl or optionally substituted heterocyclic group;

R^2 is hydrogen or halogen;

R^3 is hydrogen or lower alkyl;

R^4 and R^5 are independently hydrogen, lower alkyl, or lower cycloalkyl, or R^4 and R^5 are combined together to form lower alkylene, which is optionally interrupted by oxygen, sulfur, sulfinyl, sulfonyl or optionally mono-substituted nitrogen;

R^6 is hydroxy or protected hydroxy;

X is aryl or heterocyclic group;

Y is carbonyl or sulfonyl; and

Z is lower alkylene;

or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein

R^1 is halogen, nitro, lower alkoxy, C_6-C_{10} aryloxy optionally substituted by at least one group selected from the group consisting of halogen, cyano, nitro, amino, acylamin, lower alkylamino, carbamoyl, hydroxy, lower alkoxy, C_6-C_{10} aryloxy, lower alkyl, C_6-C_{10} aryl and heterocyclic-oxy, C_6-C_{10} arylthio, C_6-C_{10} aroyl, heterocyclic-oxy, C_6-C_{10} aryl optionally substituted by at least one group selected from the group consisting of halogen, cyano, nitro, amino, acylamino, lower alkylamino, carbamoyl, hydroxy, lower alkoxy, C_6-C_{10} aryloxy, lower alkyl, C_6-C_{10}

aryl and heterocyclic-oxy, or heterocyclic group optionally substituted by at least one group selected from the group consisting of halogen, cyano, nitro, amino, acylamino, lower alkylamino, carbamoyl, hydroxy, lower alkoxy, C_6-C_{10} aryloxy, lower alkyl, C_6-C_{10} aryl and heterocyclic-oxy;

R^4 and R^5 are independently hydrogen, lower alkyl, or lower cycloalkyl, or R^4 and R^5 are combined together to form lower alkylene, which is optionally interrupted by oxygen, sulfur, sulfinyl, sulfonyl or imino, wherein the imino is optionally mono-substituted by a group of C_6-C_{10} ar(lower)alkoxycarbonyl, lower alkylsulfonyl, C_6-C_{10} arylsulfonyl, C_6-C_{10} aroyl, mono(lower)alkylcarbamoyl, di(lower)alkylcarbamoyl or lower cycloalkylcarbonyl;

R^6 is hydroxy, tetrahydropyranyloxy or C_6-C_{10} aryl(lower)alkoxy; and

X is C_6-C_{10} aryl or heterocyclic group,

said heterocyclic group being

unsaturated 3- to 8-membered, heteromonocyclic group containing 1 to 4 nitrogen atoms,

saturated 3- to 8-membered, heteromonocyclic group containing 1 to 4 nitrogen atoms,

unsaturated bicyclic 7- to 13-membered, heterocyclic group containing 1 to 5 nitrogen atoms,

unsaturated 3- to 8-membered, heteromonocyclic group containing 1 or 2 oxygen atoms and 1 to 3 nitrogen atoms,

saturated 3- to 8-membered, heteromonocyclic group containing 1 or 2 oxygen atoms and 1 to 3 nitrogen atoms,

unsaturated bicyclic 7- to 13-membered, heterocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms,

unsaturated 3- to 8-membered, heteromonocyclic group containing 1 or 2 sulfur atoms and 1 to 3 nitrogen atoms,

saturated 3- to 8-membered, heteromonocyclic group containing 1 or 2 sulfur atoms and 1 to 3 nitrogen atoms,

unsaturated 3- to 8-membered, heteromonocyclic group containing 1 or 2 sulfur atoms,

unsaturated 3- to 8-membered, heteromonocyclic group containing 1 or 2 oxygen atoms,

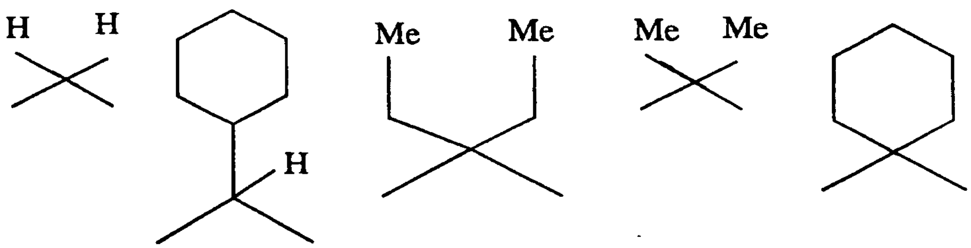
saturated 3- to 8-membered, heteromonocyclic group containing oxygen atom, unsaturated bicyclic 7- to 13-membered, heterocyclic group containing 1 or 2 sulfur atoms and 1 to 3 nitrogen atoms, or
unsaturated bicyclic 7- to 13-membered, heterocyclic group containing 1 or 2 oxygen atoms.

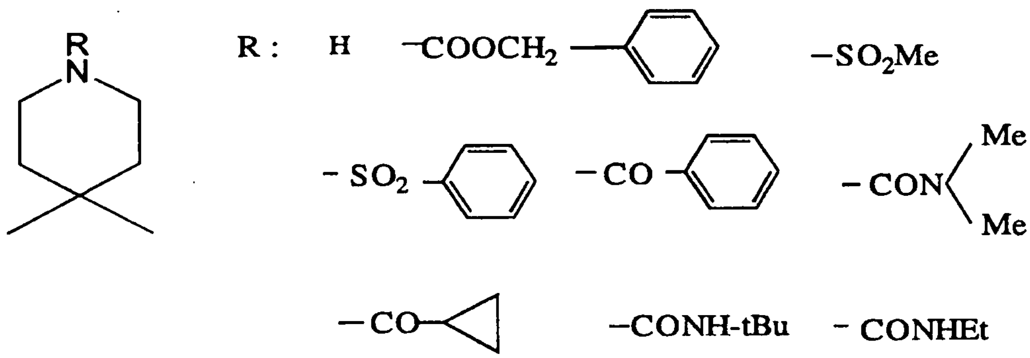
3. The compound of claim 2, wherein
R^1 is halogen; nitro; lower alkoxy; C_6-C_{10} aryloxy optionally substituted by at least one group selected from the group consisting of halogen, cyano, nitro, amino, acylamino, lower alkylamino, carbamoyl, hydroxy, lower alkoxy, C_6-C_{10} aryloxy, lower alkyl, C_6-C_{10} aryl and heterocyclic-oxy, said heterocyclic group being unsaturated 5- or 6-membered, heteromonocyclic group containing 1 to 4 nitrogen atoms; C_6-C_{10} arylthio; C_6-C_{10} aroyl; heterocyclic-oxy, said heterocyclic group being unsaturated 5- or 6-membered, heteromonocyclic group containing 1 to 4 nitrogen atoms; C_6-C_{10} aryl optionally substituted by at least one group selected from the group consisting of halogen, cyano, nitro, amino, acylamino, lower alkylamino, carbamoyl, hydroxy, lower alkoxy, C_6-C_{10} aryloxy, lower alkyl, C_6-C_{10} aryl and heterocyclic-oxy, said heterocyclic group being unsaturated 5- or 6-membered, heteromonocyclic group containing 1 to 4 nitrogen atoms; or heterocyclic group, said heterocyclic group being unsaturated 5- or 6-membered, heteromonocyclic group containing 1 to 4 nitrogen atoms, which is also optionally substituted by at least one group selected from the group consisting of halogen, cyano, nitro, amino, acylamino, lower alkylamino, carbamoyl, hydroxy, lower alkoxy, C_6-C_{10} aryloxy, lower alkyl, C_6-C_{10} aryl and heterocyclic-oxy, said heterocyclic group being unsaturated 5- or 6-membered, heteromonocyclic group containing 1 to 4 nitrogen atoms;
R^4 and R^5 are independently hydrogen, lower alkyl, or lower cycloalkyl, or R^4 and R^5 are combined together to form lower alkylene, which is optionally interrupted by oxygen, sulfur, sulfinyl, sulfonyl, imino, C_6-C_{10} ar(lower)alkoxycarbonylimino, lower alkylsulfonylimino, C_6-C_{10} arylsulfonylimino, C_6-C_{10} aroylimino, mono(lower)alkylcarbamoylimino, di(lower)alkylcarbamoylimino or lower cycloalkylcarbonylimino, and
X is C_6-C_{10} aryl or heterocyclic group,

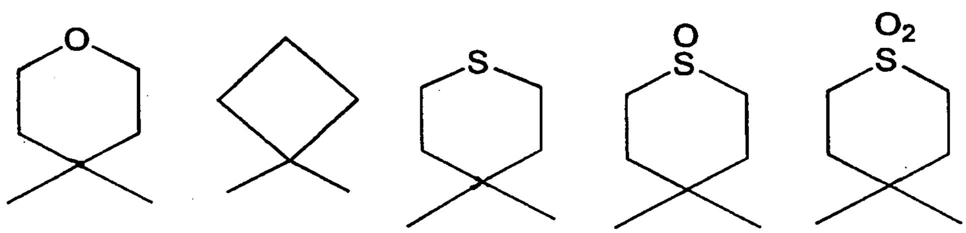
said heterocyclic group being
unsaturated 5- or 6-membered, heteromonocyclic group containing 1 to 4 nitrogen atoms, unsaturated 5- or 6-membered, heteromonocyclic group containing 1 or 2 sulfur atoms, or unsaturated 5- or 6-membered, heteromonocyclic group containing 1 or 2 oxygen atoms.

4. The compound of claim 3, wherein
R^1 is halogen; nitro; lower alkoxy; phenoxy or naphthyloxy, each of which is optionally substituted by at least one group selected from the group consisting of halogen, cyano and lower alkyl; phenylthio; benzoly; pyridyloxy; phenyl optionally substituted by halogen; or pyridyl,
R^4 and R^5 are independently hydrogen, lower alkyl, or lower cycloalkyl, or R^4 and R^5 are combined together to form lower alkylene, which is optionally interrupted by oxygen, sulfur, sulfinyl, sulfonyl, imino, phenyl(lower)alkoxycarbonylimino, lower alkylsulfonylimino, phenylsulfonylimino, benzoylimino, mono(lower)alkylcarbamoylimino, di(lower)alkylcarbamoylimino or lower cycloalkylcarbonylimino,
R^6 is hydroxy, tetrahydropyranyloxy or phenyl(lower)alkoxy, and
X is phenyl, pyridyl, thienyl ro furyl.

5. The compound of claim 4, wherein
R^1 is halogen; nitro; lower alkoxy; phenoxy, naphthyloxy, halophenoxy, cyanophenoxy, lower alkylphenoxy, phenylthio; benzoyl; pyridyloxy; halophenyl; or pyridyl;
R^4 and R^5 are combined together to form a group of the formula selected from the group consisting of the following formulas:

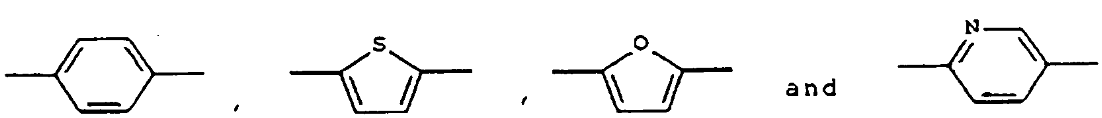






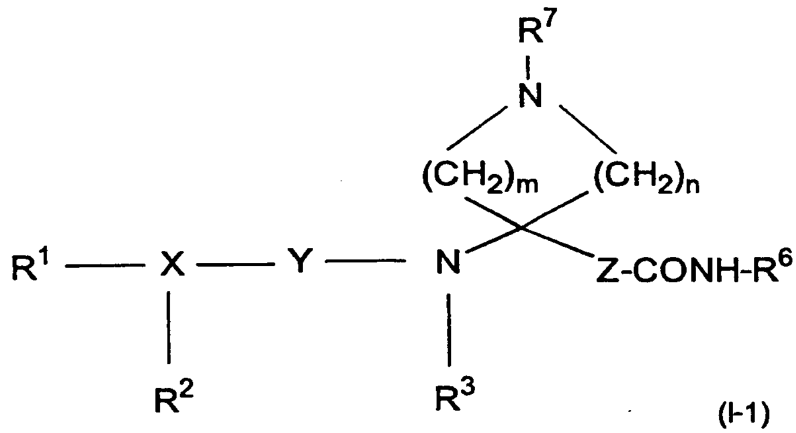
R^6 is hydroxy, and

X is a group selected from the group consisting of



6. A process for the preparation of the compound of claim 1 or salt thereof, which comprises,

(1) removing the imino-protective group of a compound of the formula (I-1)



(I-1)

wherein

R^1 is halogen, nitro, lower alkoxy, optionally substituted aryloxy, arylthio, aroyl, heterocyclic-oxy, optionally substituted aryl or optionally substituted heterocyclic group;

R^2 is hydrogen or halogen;

R^3 is hydrogen or lower alkyl;

R^6 is hydroxy or protected hydroxy;

X is aryl or heterocyclic group;

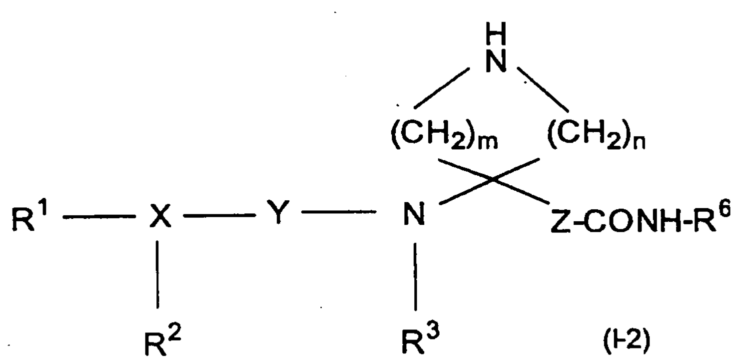
Y is carbonyl or sulfonyl;

Z is lower alkylene;

R^7 is imino-protective group; and

m and n are independently an integer of 1 to 5, provided that $2 \leqq m+n \leqq 6$;

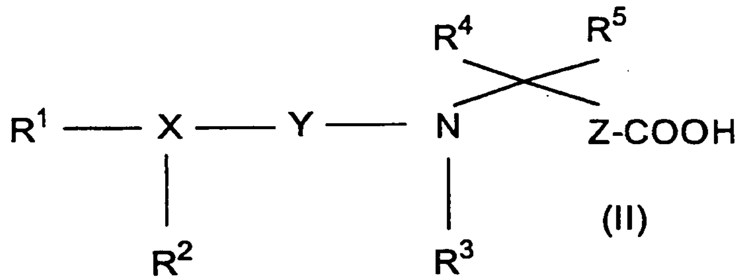
or a salt thereof, to give a compound of formula (I-2):



(I-2)

wherein each symbol is as defined above or a salt thereof;

(2) reacting a compound of the formula (II):



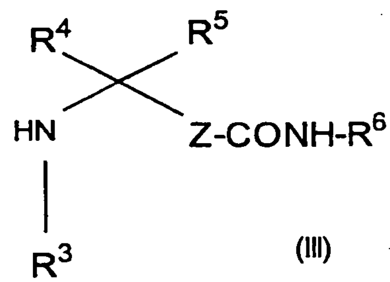
(II)

wherein R^4 and R^5 are independently hydrogen, lower alkyl, or lower cycloalkyl, or R^4 and R^5 are combined together to form lower alkylene, which is optionally interrupted by oxygen, sulfur, sulfinyl, sulfonyl or optionally mono-substituted nitrogen, and other symbols are each as defined above, or its reactive derivative at the carboxy group, or a salt thereof, with a compound:

$$H_2N\text{-}R^6$$

wherein R^6 is as defined above, or its reactive derivative at the amino group, or a salt thereof to give the compound of the formula (I);

(3) reacting a compound (III):



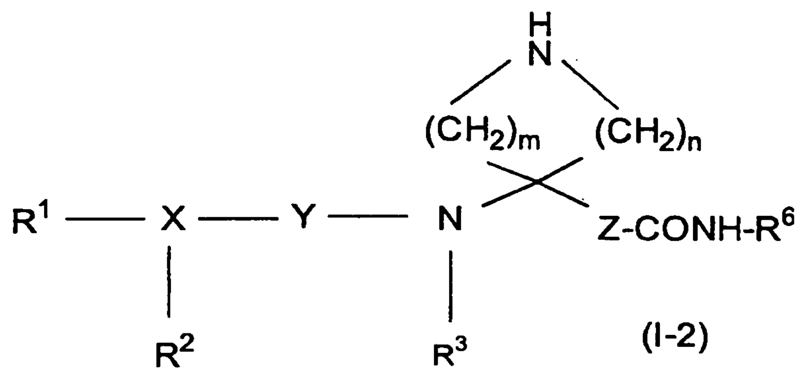
(III)

wherein each symbol is as defined above, or a salt thereof with a compound

$$R^1\text{-}X(R^2)\text{-}Y\text{-}L$$

wherein L is a leaving group and other symbols are each as defined above, or a salt thereof to give the compound of the formula (I);

(4) reacting a compound of the formula (I-2):

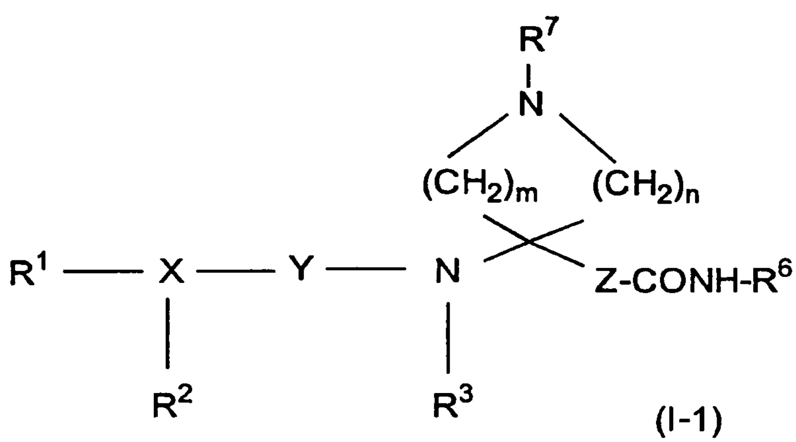


(I-2)

wherein each symbol is as defined above, or a salt thereof with a compound:

R^7-L

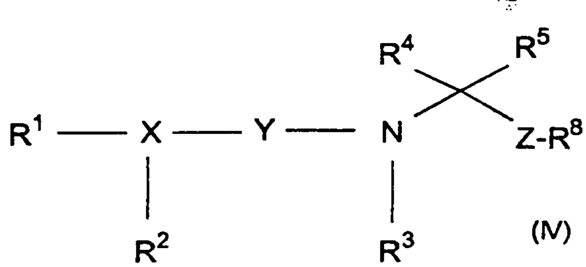
wherein each symbol is as defined above, or a salt thereof, to give a compound of the formula (I-1):



(I-1)

wherein each symbol is as defined above, or a salt thereof;

(5) reacting a compound of the formula (IV):

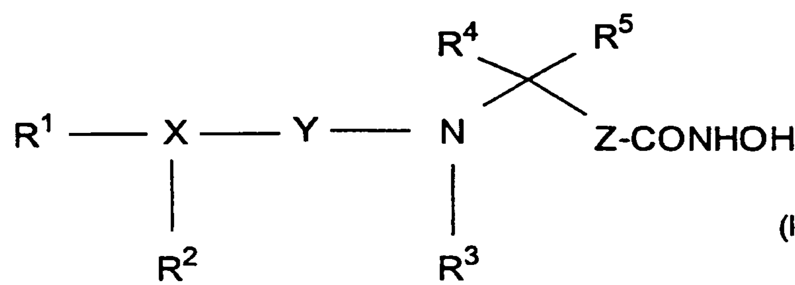


(IV)

wherein R^8 is a protected carboxy and other symbols are each as defined above, or a salt thereof, with a compound:

$$H_2N\text{-}OH$$

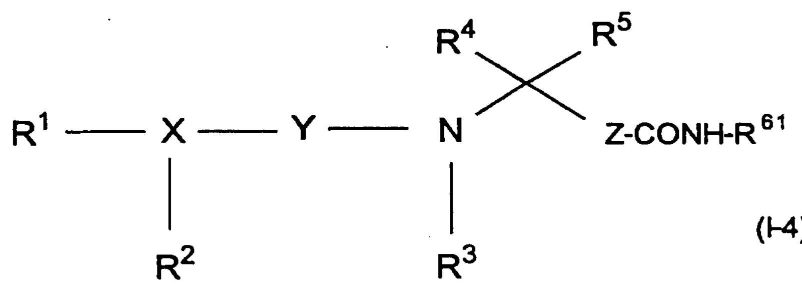
or a salt thereof; to give a compound of the formula (I-3):



(I-3)

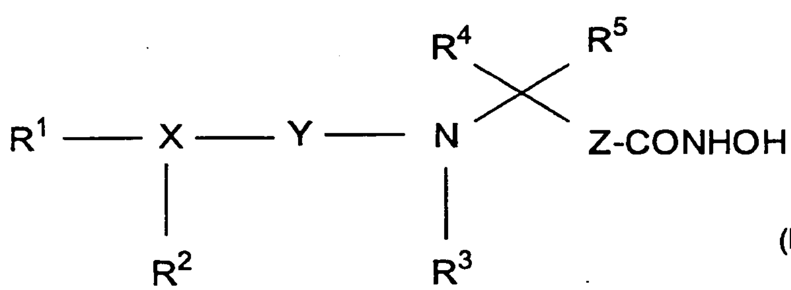
wherein each symbol is as defined above, or a salt thereof; or

(6) eliminating the hydroxy-protective group of a compound of the formula (I-4):



(I-4)

wherein R^{61} is a protected hydroxy, and other symbols are each as defined above, or a salt thereof, to give a compound of the formula (I-3):



(I-3)

wherein each symbol is as defined above, or a salt thereof.

7. A pharmaceutical composition which comprises the compound of Claim 1 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or excipient.

8. Use of the compound of Claim 1 or a pharmaceutically acceptable salt thereof as a medicament.

9. Use of the compound of Claim 1 or a pharmaceutically acceptable salt thereof as an inhibitor of matrix metalloproteinases (MMP) or tumor necrosis factor α (TNFα).

10. Use of the compound of Claim 1 or a pharmaceutically acceptable salt thereof for manufacturing a medicament for treating and/or preventing MMP- or TNFα-mediated diseases.

11. A method for treating and/or preventing MMP- or TNFα-mediated diseases which comprises administering the compound of Claim 1 or a pharmaceutically acceptable salt thereof to a human being or an animal.

INTERNATIONAL SEARCH REPORT

In .tional Application No
PCT/JP 00/02508

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C259/06 C07C311/29 C07D405/12 C07D307/68 C07D309/12
C07D213/64 A61K31/165 A61K31/445 A61P17/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	MANFRED JUNG ET AL.: "Amide Analogues of Trichostatin A as Inhibitors of Histone Deacetylase and Inducers of Terminal Cell Differentiation" JOURNAL OF MEDICINAL CHEMISTRY., vol. 42, no. 22, 4 November 1999 (1999-11-04), pages 4669-4679, XP002144226 AMERICAN CHEMICAL SOCIETY. WASHINGTON., US ISSN: 0022-2623 page 4671, table 1, examples 5h - 71; page 4676, column 2, middle - page 4678, column 1, line 4 ---	1-8

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 August 2000	28/08/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Zervas, B

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP 00/02508

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 99 19296 A (ONO PHARMACEUTICALS) 22 April 1999 (1999-04-22) pages 170-192,459,460; claims -& EP 1 024 134 A (ONO PHARMACEUTICAL) 2 August 2000 (2000-08-02) pages 146-165,379; claims	1-11
X	& ZA 9 809 113 A (ONO PHARMACEUTICAL) 14 April 1999 (1999-04-14) ---	1-11
L	DATABASE CAPLUS 'Online! Chemical Abstracts Service; Abstract 130:311803, XP002144337 Remark: The document discloses the publication date of the above cited document ZA 9 809 113 (cited as &-document of WO 99 19296), which was not available as paper copy at the time of the search abstract -& CHEMICAL ABSTRACTS, vol. 130, no. 23, 7 June 1999 (1999-06-07) Columbus, Ohio, US; abstract no. 311803y, KANJI TAKAHASHI ET AL.: "Preparation of aminobutanoic acid derivatives as inhibitors of matrix metalloproteinases" page 705; column 2; XP002144336 abstract ---	
X	US 4 407 822 A (LOUIS LAFON) 4 October 1983 (1983-10-04) column 2, line 16 - line 54 ---	1-6
A	WO 96 27583 A (PFIZER) 12 September 1996 (1996-09-12) claims; examples ---	1,7-11
A	WO 97 20824 A (AGOURON PHARMACEUTICALS) 12 June 1997 (1997-06-12) cited in the application claims; examples -----	1,7-11

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. ional Application No
PCT/JP 00/02508

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